Review Article

Neurokinin-1 Receptor Antagonists as Antitumor Drugs in Gastrointestinal Cancer: A New Approach

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ABSTRACT

Gastrointestinal (GI) cancer is the term for a group of cancers affecting the digestive system. After binding to the neurokinin-1 (NK-1) receptor, the undecapeptide substance P (SP) regulates GI cancer cell proliferation and migration for invasion and metastasis, and controls endothelial cell proliferation for angiogenesis. SP also exerts an antiapoptotic effect. Both SP and the NK-1 receptor are located in GI tumor cells, the NK-1 receptor being overexpressed. By contrast, after binding to the NK-1 receptor, NK-1 receptor antagonists elicit the inhibition (epidermal growth factor receptor inhibition) of the proliferation of GI cancer cells in a concentration-dependent manner, induce the death of GI cancer cells by apoptosis, counteract the Warburg effect, inhibit cancer cell migration (counteracting invasion and metastasis), and inhibit angiogenesis (vascular endothelial growth factor inhibition). NK-1 receptor antagonists are safe and well tolerated. Thus, the NK-1 receptor could be considered as a new target in GI cancer and NK-1 receptor antagonists (eg, aprepitant) could be a new promising approach for the treatment of GI cancer.

Key Words: Colorectal cancer, gastric cancer, hepatoblastoma, esophageal carcinoma, pancreatic cancer

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Gastrointestinal (GI) cancer includes cancers of esophagus, gallbladder, liver, pancreas, stomach, small intestine, bowel (large intestine or colon and rectum), and anus. GI cancer is the second most common form of cancer. In the USA, in 2013, there were 290,000 new cases of GI cancer, and 144,000 persons suffering this kind of cancer died. The global rate of mortality for GI cancer is 49.5%.[1] Currently, the basis for the treatment of GI cancer are cytostatic drugs, and the lack of selectivity of these and their numerous side effects are well known. The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults has been estimated to be 2.3% and 2.1% in Australia and USA, respectively.[2] Accordingly, it is crucial, to discover and test curative drugs exhibiting minimal side effects in the treatment of GI cancer.

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In recent years, our knowledge of the expression and secretion of peptides by tumor cells has expanded because it has been shown that peptides regulate tumor cell and mass proliferations. Thus, after binding to the neurokinin-1 (NK-1) receptor [Figure 1a and b], substance P (SP) acts as a mitogen in human GI cancer cell lines such as pancreatic cancer, gastric and colon carcinoma, hepatoblastoma, and cholangiocarcinoma.[3-6] NK-1 receptors are overexpressed in GI cancer[3-5] [Table 1]. NK-1 receptor antagonists exert an antitumor action against GI cancer[3-6] [Table 2]. *In vitro* and *in vivo* the drug aprepitant (an NK-1 receptor antagonist) also exerts an antitumor action against human GI cancer cell lines and tumors[5,7] [Figure 2 and Table 2]. In light of the foregoing, our aim here is to update information about the role played by the SP/NK-1 receptor system in GI cancer.

THE SUBSTANCE P/NK-1 RECEPTOR SYSTEM

The undecapeptide substance P (SP) is derived from the preprotachykinin-A gene and belongs to the tachykinin family of peptides. The biological actions of tachykinins are mediated by three receptors (NK-1, NK-2, and NK-3). SP is the natural ligand with the highest affinity for the NK-1 receptor[8] and hence the biological action of the undecapeptide is mainly mediated by this receptor. SP is ubiquitous throughout human body: The undecapeptide is widely distributed in all tissues and body fluids (eg, blood, cerebrospinal fluid) and this means that it can regulate cell function through autocrine, paracrine, endocrine, and/or neuroendocrine mechanisms.[9] After binding to the NK-1 receptor SP regulates many pathophysiological processes (eg, inflammation) in a concentration-dependent manner.[9] SP regulates the proliferation of cancer cells, exerts an antiapoptotic effect, stimulates the migration of tumor cells for invasion and metastasis, and stimulates neoangiogenesis[8] [Figure 3a].

Via the NK-1 receptor, SP generates second messengers, triggering a variety of effector mechanisms that regulate cellular excitability and function[8] [see Figure 3a]. SP activates members of the mitogen-activated protein kinase (MAPK) cascade via the NK-1 receptor, including p38MAPK and extracellular signal-regulated kinases 1 and 2 (ERK1/2). The presence of a functional epidermal growth factor receptor (EGFR) kinase domain is required for SP-induced MAPK activation,[10] and stimulation by SP of the NK-1 receptor increases the phosphorylation and activity of Akt or protein kinase B (EC 2.7.11.1), which becomes activated by phosphatidyl-3-kinase (PI3K). The activation of Akt suppresses apoptosis,[11,12] whereas treatment with NK-1 receptor antagonists elicits it, because these antagonists block the increase in phosphorylation triggered by SP. The blockade of NK-1 receptors by the NK-1 receptor antagonist L-733,060 inhibits the basal kinase activity of Akt; this is important, because the basal activity of Akt is associated with a poor prognosis.[13] After binding to the NK-1 receptor, SP exerts other pathophysiological effects: The undecapeptide induces glycogen breakdown; it stimulates the release of interleukins, taurine, and glutamate; it induces the formation of inositol phosphate; and regulates glutamate and K^+ transport.[8] The release of interleukins, taurine, and glutamate by tumor cells induces an inflammatory process, increasing the levels of SP and hence increasing tumor cell proliferation (because SP is a mitogenic agent in tumor cells).

Cancer cells produce energy by means of a high rate of glycolysis followed by lactic acid fermentation: This is known as the Warburg effect. Growing tumor cells have glycolytic rates up to 200 times higher than those of their

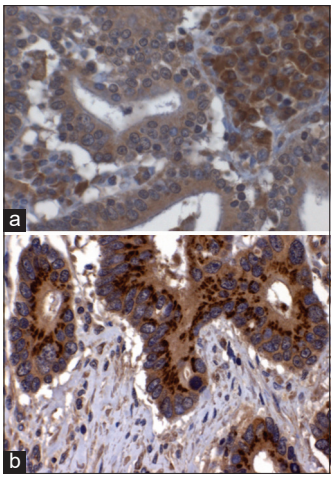

Figure 1: Expression of the NK-1 receptor in human primary gastric (a) and colon (b) adenocarcinomas. (a) NK-1 receptors can be observed on the cytoplasm of the epithelial cells of the tumor glands and in numerous stromal elements (50×). (b) Presence of NK-1 receptors on the cytoplasm of the epithelial cells of the tumor glands. Note also an intense granular cytoplasm staining showing NK-1 receptors (50×)

Table 1: Presence of SP and NK-1 receptors in human GI tumor cells and samples

Tumor cells/samples	Substance P	NK-1 receptor
Colon carcinoma	Not studied	+
Gastric carcinoma	Not studied	+
Hepatoblastoma	+	+
Pancreatic carcinoma	Not studied	+
Hepatocellular carcinoma	Not studied	+
Cholangiocarcinoma	+	+
Eophageal carcinoma	+	+

GI: Gastrointestinal, NK-1: Neurokinin-1

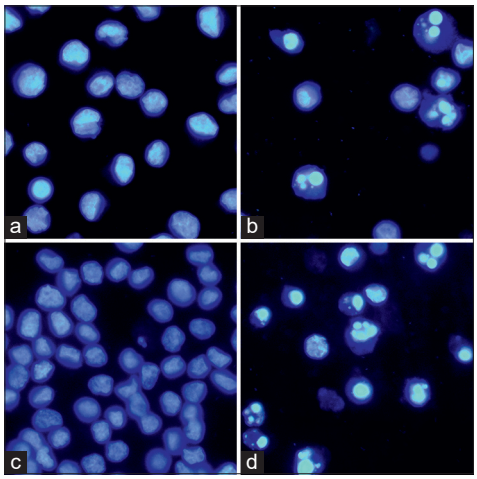

Figure 2: Gastric (a and b) and colon (c and d) carcinoma culture cells (100×). (a and c) Control. (b and d) Cells treated with the NK-1 receptor antagonist (L-733,060). Note apoptotic figures: Chromatin condensation and nuclear fragmentation are observed

Table 2: GI tumor cells, cytotoxicity, mitogenic effect of SP and NK-1 receptor isoforms (*approximately)

Tumor	Cell line	L-732,138		L-733,060		Aprepitant		SP nM	NK-1 receptor isoforms kDa
		IC_{50} μM	IC_{100} μM	IC_{50} μM	IC_{100} μM	IC_{50} μM	IC_{100} μM		
Colon carcinoma	SW-403			14.5	25.8	30.5	60.5	50	75, 58, 46, 34
Gastric carcinoma	23132/87			14.3	29.6	24.2	52.5	10	75, 58, 46, 34
Hepatoblastoma	HepT1	42		16		31.1		10-50	58, 50
	HUH6	43		11		33.18			
	HepG2	101		9		38.61			
Pancreas carcinoma	PA-TU-8902			18.1	38.4	31.2	63	100	75, 58, 46, 33
	CAPAN-1			20	39.7	27.4	52		
Collangiocarcinoma	Mz-ChA-1 SG231 HuCC-T1								13
	TFK-1			20-100*				1 nM-1 μM	
	HuH-28, CCLP1								

GI: Gastrointestinal, NK-1: Neurokinin-1, SP: Substance P

normal tissues of origin. In tumor cells, SP produces glycogen breakdown and then these cells use glucose to increase their metabolism. This mechanism could in part explain the Warburg effect [Figure 3a]. NK-1 receptor antagonists block glycogen breakdown in tumor cells, counteracting the Warburg effect [Figure 3b]. This means that NK-1 receptor antagonists produces the death of tumor cells by starvation.

SP is located in the nuclei of tumor cells. This suggests that the undecapeptide might act as an epigenetic factor,[14] regulating several transcription factors involved in cancer development and progression such as ERK1/2, c-myc, c-fos, c-jun, AP-1, and NF-κB.[15] In the future, this should be investigated in depth.

In cancer treatment, monoclonal antibodies (eg, cetuximab and panitumumab, specific for RAS wild-type tumors) targeting EGFR and monoclonal antibodies (eg, bevacizumab) targeting vascular endothelial growth factor (VEGF) have been used.[16] The blockade of SP induces apoptosis in colon cancer and in other types of cancers [Figure 2b and d], this effect being accompanied by a decrease in the MAPK signaling pathways. SP abrogation decreases the steady-state of Her2 and EGFR, suggesting that SP-mediated signaling is important for the basal activity of these ErbB receptors. Accordingly, both the blockade of cell cycle progression and the inhibition of several cell cycle-related proteins, including mTOR, have been observed. SP inhibition also induces cell death in cancer cell lines resistant to lapatinib and trastuzumab that show increased levels of active Her2, suggesting that this therapeutic approach could also be effective for cancers resistant to current anti-ErbB therapies.[17] SP promotes the proliferation of triple negative breast cancer (TNBC) cells, whereas both the NK-1 receptor antagonist L-733,060 [Figure 2b and d] and application of the siRNA methodology inhibit cell proliferation and induce apoptosis. SP could also enhance expression of phosphorylation (p)-EGFR and EGFR, and activate p-Akt and p-ERK. NK-1-siRNA could decrease p-EGFR, p-Akt, and p-ERK. In the presence of cetuximab, SP could stimulate cell proliferation and activate p-EGFR, but not in the presence of erlotinib. The results suggest that the NK-1 receptor may regulate TNBC proliferation through EGFR phosphorylation, and that the curative effect of EGFR monoclonal antibodies may be affected by activation of the NK-1 receptor.[18] VEGF stimulates vasculogenesis and angiogenesis in tumors and hence anti-VEGF antibodies [eg, bevacizumab: A full-length IgG1 approved for the treatment of specified cancer indications, and ranibizumab: An affinity-matured antibody Fab domain approved for use in age-related macular degeneration (AMD)] have been tested. In clinical trials both antibodies have been seen to be therapeutically useful in that they block VEGF-induced angiogenesis.[19] VEGF is regulated by SP and, in cholangiocarcinoma, NK-1 receptor antagonists decrease the level of VEGF[6] [Table 3].

THE SUBSTANCE P/NK-1 RECEPTOR SYSTEM IN GI CANCER

Upper gastrointestinal cancer

Esophageal squamous cell carcinoma (ESCC) tissues express a higher density of SP-positive nerve fibers and an overexpression of the NK-1 receptor [Table 1]. This density is correlated with the tumor size and with the lymph node metastasis. SP promotes ESCC proliferation and migration by modulating the level of intracellular calcium.[20]

Hypermethylation of the tachykinin-1 (*TAC1*) gene has been linked to human esophageal neoplastic transformation. *TAC1* gene promoter hypermethylation is a common event in major histological types of human esophageal carcinoma; it correlates with other progression risk factors in esophageal adenocarcinogenesis, occurs early, and is a tissue biomarker of a poor prognosis in human esophageal carcinoma. *TAC1* promoter DNA is a potential biomarker for the diagnosis of esophageal carcinoma.[21]

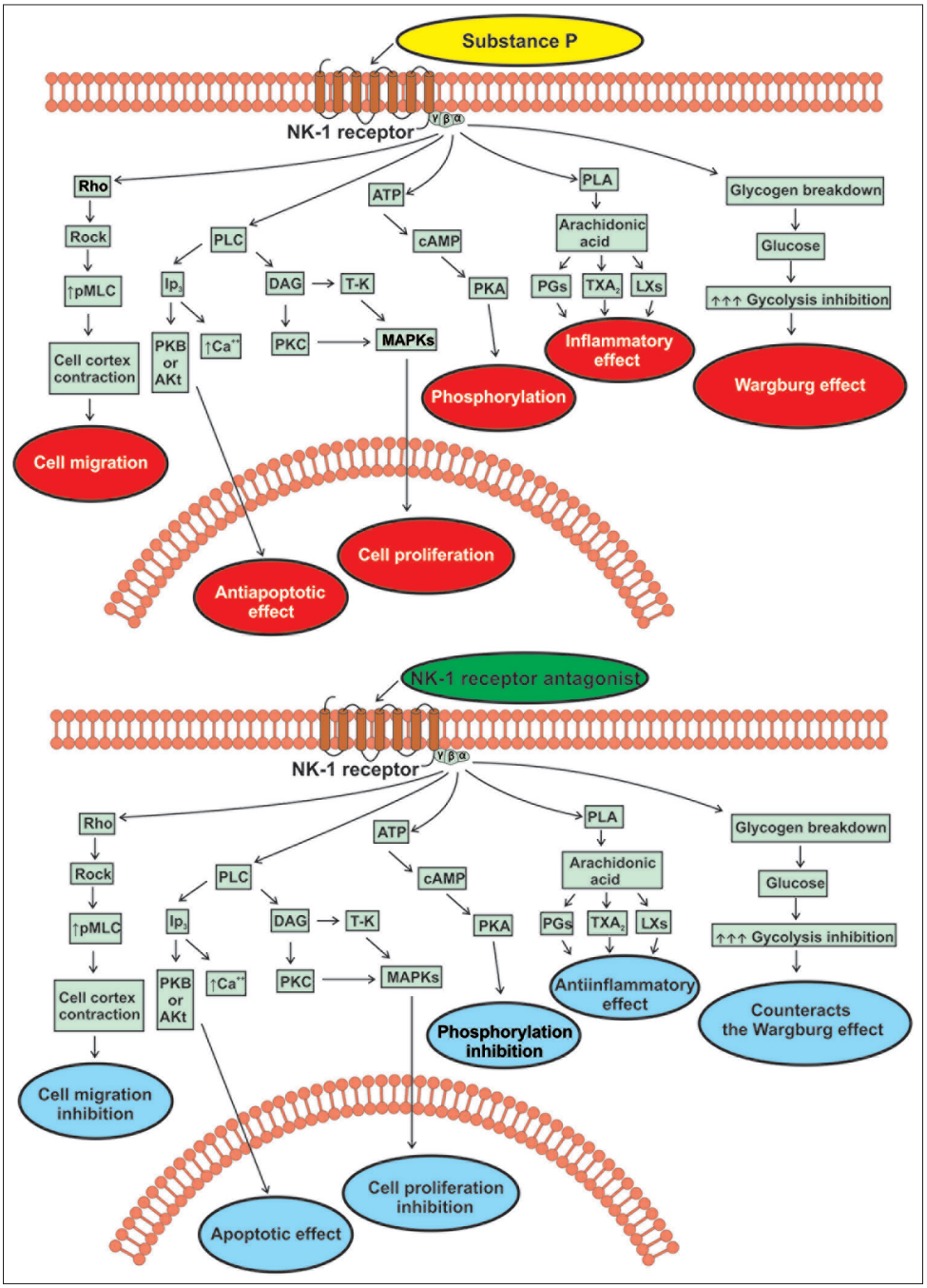

Figure 3: Cell signaling pathways downstream of the NK-1 receptor. (a) Activation of this receptor by SP. (b) NK-1 receptor antagonists block the pathways mediated by SP. ATP = Adenosine triphosphate, cAMP = Cyclic adenosine monophosphate, DAG = Diacilglicerol, Ip_3 = Inositol triphosphate, LXs = Leukotrienes, MAPKs = Mitogen-activated protein kinase, PGs = Prostaglandins, PKA = Protein kinase A, PKB or AKt = Protein kinase B, PKC = Protein kinase C, PLA = Phospholipase A, PLC = Phospholipase C, pMLC = Myosin regulatory light chain phosphorylation, T-K = Tyrosine-kinase, TXA_2 = Thromboxane A_2

The administration of high doses of SP favors gastric carcinogenesis induced by *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine, this effect being associated with the stimulation of the proliferation of antral epithelial cells.[22] Myenteric denervation decreases the number and size of gastric adenocarcinomas, this decrease being more evident when denervation is associated with pyloroplasty.[23] The authors of an *in vitro* study have reported that SP promotes proliferation, adhesion, migration, and invasion of MKN45 gastric cancer cells.[24] In human gastric cancer the presence of both SP-containing nerves and NK-1 receptors has been reported, and it has been suggested that the number

Table 3: Cytostatic therapeutic effects versus NK-1 receptor antagonists

Organ/site	Classic cytostatics	NK-1 receptor antagonists
Cell specificity	Nonspecific cytotoxicity	Specific cytotoxicity against tumor cells, through the NK-1 receptor (upregulation and overexpression)
Tumor	Mitogenesis inhibition	Mitogenesis inhibition (EGFR inhibition)
	Cell death by necrosis	Cell death by apoptosis
		Counteract the Warbur effect
		Angiogenesis inhibition (VEGF inhibition)
		Inhibition of the migration of tumor cells. Prevents invasion and metastasis
		Decrease permeability of the blood-brain barrier (preventing brain metastasis)
Central nervous system	Emesis	Antiemetic
	Anxiety	Anxiolytic
	Seizure	Anticonvulsant
	Encephalopathy	Neuroprotector
Peripheral nervous system	Polyneuropathy	Neuroprotector
Liver	Hepatotoxicity	Hepatoprotector
Kidney	Nephrotoxicity	Nephroprotector
Systemic	Inflammatory	Anti-inflammatory

EGFR: Epidermal growth factor receptor, VEGF: Vascular endothelial growth factor, NK-1: Neurokinin-1

of SP-positive nerves would be related to gastric cancer progression.[24] It is also known that the 23132/87 gastric adenocarcinoma cell line expresses isoforms of the NK-1 receptor; that SP, at nanomolar concentration, elicits gastric cancer cell proliferation; that NK-1 receptor antagonists (L-733,060, aprepitant), at micromolar concentration, inhibit gastric cancer cell proliferation, and that at certain doses inhibit 100% of cells and that gastric cancer cells die by apoptosis[4] [Table 2 and Figure 2b].

Colorectal cancer

The SW-403 human colon adenocarcinoma cell line expresses isoforms of the NK-1 receptor; SP (nanomolar concentration) elicits colon cancer cell proliferation, and NK-1 receptor antagonists (μM concentration) fully inhibit colon cancer cell proliferation; these cells die by apoptosis[4] [Table 2 and Figure 2d]. Colon cancer samples express both the full-length and the truncated forms of the NK-1 receptor[25] [Table 1]. The latter form increases the growth of cancer cells, stimulating the synthesis of cytokines, and mediates malignancy in tumor cells, whereas the full-length form regulates the slow growth of tumor cells.[8] Cytokines activate NF-κB, which upregulates the truncated form but slightly increases the full-length form. In a population-based case–control study, which include 394 cases of colorectal cancer and 393 cancer-free controls, it was concluded that tachykinin, precursor 1, tachykinin receptor 1, and tachykinin receptor 2 genes were involved in the risk of colorectal cancer and that tachykinins pathway genes may participate in the development of colorectal cancer.[26]

The NK-1 receptor antagonist aprepitant exerts a significant antiproliferative effect against both LiM6 and DLD1 human colon cancer cell lines. In this case, it seems that an inhibition of the canonical Wnt pathway occurs, as seen in decreased super TOP/FOP levels and increased membrane stabilization of β-catenin. This effect was independent of baseline Wnt activity and the mutational status of β-catenin. NK-1 receptor antagonists exert an antitumor action against colon cancer stem cells (CSC). The NK-1 receptor could be an anticancer target for the treatment of colon cancer, and NK-1 receptor antagonists could potentially serve as future anticancer drugs because this anticancer effect occurs in both primary cancer cells and CSC-like cells. In addition, this treatment elicits a robust inhibition of canonical Wnt signaling by targeting the SP/NK1 receptor-signaling cascade.[27]

Hepatic, pancreatic, and biliary tract cancers

In some human hepatocellular carcinoma samples, the expression of NK-1 receptors has been reported, this expression being mainly located in intratumoral and peritumoral blood vessels.[28] Later, when more selective methods were applied, the number of cases of hepatocellular carcinoma expressing the NK-1 receptor increased considerably [Table 1]. Thus, human hepatoblastoma cells and samples express NK-1 receptors; human hepatoblastoma HepT1, HepG2, and HuH6 cell lines overexpress the truncated form of the NK-1 receptor compared with normal cells; SP (nanomolar concentration) elicits hepatoblastoma cell proliferation; NK-1 receptor antagonists (L-733,060, L-732,138, aprepitant) at micromolar concentrations fully inhibit hepatoblastoma cell proliferation, and hepatoblastoma cells die by apoptosis[5] [Table 2].

In a study using autoradiography with ^{125}I-labelled Bolton–Hunter only 1/9 cases of pancreatic cancers expressed the NK-1 receptor.[29] By contrast, some years later, with a different method (real-time quantitative RT-PCR), a marked increase was observed in mRNA NK-1 receptor levels in most of the cancer samples, as confirmed by Western blot analyses. Human pancreatic cancer cells and samples express NK-1 receptors[3,30] [Table 1]. CAPAN-1 and PA-TU 8902 pancreatic adenocarcinoma cell lines express similar isoforms of the NK-1 receptor; SP (nanomolar concentration) favors pancreatic cancer cell proliferation; NK-1 receptor antagonists (L-733,060, aprepitant) at micromolar concentrations fully inhibit pancreatic cancer cell proliferation, and pancreatic cancer cells die by apoptosis[3,7] [Table 2]. In most tumors

investigated, NK-1 receptors have been found in intra- and peritumoral blood vessels. This is very important with regard to the involvement of the NK-1 receptor in angiogenesis.[29] NK-1 receptors have also been located in nerves, ganglia, and inflammatory cells. It has been reported that tumor cells express more NK-1 receptors than nontumor cells; that, in comparison with normal cells, human pancreatic cancer cell lines overexpress the NK-1 receptor; that the highest expression of NK-1 receptors was observed in the most malignant phenotypes of tumors and this was associated with advanced tumor stages and a poorer prognosis; and that tumor samples from patients with advanced tumor stages exhibit higher NK-1 receptor levels.[8] In pancreatic cancer, SP is involved in perineural invasion, and in pancreatic cancer cells the peptide induces proliferation and invasion and the expression of matrix metalloproteinase (MMP)-2.[30] SP also promotes neurite outgrowth and the migration of pancreatic cancer cell clusters to the dorsal root ganglia of newborns.[30]

In cholangiocarcinoma (CCA), SP promotes cholangiocyte growth during cholestasis by activating the NK-1 receptor. SP is deactivated by membrane metalloendopeptidases (MME). Human CCA cell lines exhibit increased expression of *TAC1* and the NK-1 receptor [Table 1], along with reduced levels of MME compared with nonmalignant cholangiocytes, resulting in a subsequent increase in SP secretion. *In vitro*, SP treatment increases CCA cell proliferation, which is blocked by the NK-1 receptor antagonist L-733,060 [Table 2]. Treatment with L-733,060 alone inhibits CCA proliferation *in vitro* and *in vivo*. Xenograft tumors derived from MME-overexpressed human Mz-ChA-1 CCA cells have a slower growth rate than those derived from control cells. The expression of PCNA, CK-19, and VEGF-A is decreased, whereas MME expression increases in xenograft tumors treated with L-733,060 or in MME-overexpressed xenograft tumors as compared with controls. This suggests that the SP secreted by CCA [Table 1] promotes CCA growth via an autocrine pathway. By contrast, the use of NK-1 receptor antagonists may be important for the management of CCA.[6]

CHRONIC INFLAMMATION: THE SUBSTANCE P/ NK-1 RECEPTOR SYSTEM PROMOTES GI CANCER

The tandems of chronic esophagitis/esophageal cancer, chronic gastritis/gastric cancer, ulcerative colitis/colon cancer, chronic hepatitis/hepatocarcionoma, and chronic pancreatitis/pancreatic cancer are well known. The inflammatory process is a cofactor of carcinogenesis. It is known that proinflammatory cytokines are involved in malignant progression[31]; that the features of neurogenic inflammation are an increase in vascular permeability, plasma extravasation, edema formation, and leukocyte infiltration; and that SP is the main mediator in neurogenic inflammation. In inflammatory processes SP contributes to leukocyte recruitment[32]; the peptide activates NF-κB, a transcription factor involved in the control of cytokine expression,[33] and it stimulates human peripheral blood monocytes to produce inflammatory cytokines, including IL-1, IL-6, IL-12, and TNFα.[9]

The risk of pancreatic cancer is very high in subjects with chronic pancreatitis and appears to be independent of gender, country, or type of pancreatitis. In both chronic pancreatitis and pancreatic cancer, the NK-1 receptor is overexpressed.[34] The protein level of the full NK-1 receptor is increased by 40% in high-grade dysplasia in chronic ulcerative colitis and colon carcinoma in comparison with quiescent colitis, whereas the expression of truncated NK-1 receptors is increased 14-fold.[25] The number of NK-1 receptors in cancer tissue (sporadic colorectal cancer and colitis-associated colorectal cancer) and sporadic dysplasia is higher than in normal tissues. It seems that the expression of NK-1 receptors and p-EGFR positivity with vitamin D receptor negativity could be used to identify areas of sporadic colorectal neoplasia.[35]

SP promotes both neurogenic inflammation and pancreatic-, gastric-, and colon carcinoma-cell proliferation[3,4] [Table 2]. The data suggest that overexpression of the NK-1 receptor could be involved in chronic pancreatitis and in chronic ulcerative colitis-associated cancer. The overexpression of NK-1 receptor could be used as a biomarker to identify patients at risk of developing GI cancer [Table 1] and could serve as a therapeutic target in the treatment of GI cancer-inducing chronic inflammation.

NK-1 RECEPTOR ANTAGONISTS IN GI CANCER

NK-1 receptor antagonists belong to a broad group of heterogeneous compounds. There are two groups: Peptide and nonpeptide NK-1 receptor antagonists. The former suffer from a number of drawbacks (eg, poor potency, neurotoxicity, mast cell-degranulating activity). *In vitro* and *in vivo*, peptide NK-1 receptor antagonist exerts an antitumor effect (eg, against pancreatic cancer) and inhibits angiogenesis.[36,37] It has been reported that [D-Arg-Pro-Lys-Pro-D-Phe-Gln-D-Trp-Phe-D-Trp-Leu-Ac5c-NH_2] SP analog antagonist in combination therapy with three neuropeptide analog antagonists have antitumor effect *in vitro* and *in vivo* against GI cancer (colon, pancreas, and duodenum) and other non-GI cancers.[38]

The mechanism of action of NK-1 receptor antagonists is by a blockade of the pathophysiological actions mediated by SP when it binds to the NK-1 receptor in a concentration-dependent manner [Figure 3b]. Nonpeptide NK-1 receptor antagonists include the following compounds: Perhydroisoindolones, steroids, tryptophan-based (L-732,138) [Table 2], benzylamino and benzylether quinuclidine, benzylether piperidines

(L-733,060) [Table 2], and benzylamino piperidines. Some of these nonpeptide NK-1 antagonists have been used in clinical trials and found to be safe; this is the case for the drug aprepitant [Table 2] and its prodrug fosaprepitant.[39] Nonpeptide NK-1 receptor antagonists also exert beneficial pharmacological effects[9] [Table 3]. However, the only nonpeptide NK-1 receptor antagonists currently used in clinical practice (for the treatment of vomiting and postoperative nausea and vomiting and acute and delayed chemotherapy-induced nausea) are aprepitant (Emend, MK-869, L-754,030) and its intravenously administered prodrug fosaprepitant (Ivemend, MK-0517, L-758,298).[39] The release of SP is induced by chemotherapy, and aprepitant blocks the unwanted actions exerted by the undecapeptide.[40] The safety of aprepitant (eg, 300 mg/day is well tolerated) has been proved in many human clinical trials and in human fibroblasts, in which the IC_{50} is three times higher than the IC_{50} for cancer cells.[7] The IC_{50} for nontumor cells is 90 μM but the IC_{100} for tumor cells (including GI cancer) is approximately 60 μM.[7] Judging by the concentration of aprepitant that exerts an antitumor effect in *in vitro* experiments, the doses of the drug that could be used in clinical practice would be very low (40–50 mg/kg/day for cancer treatment) in comparison with the doses used in carcinogenicity studies for aprepitant (125–2000 mg/kg/day for carcinogenesis).[1,8] The safety of NK-1 receptor antagonists is also due to the fact that they only act when the NK-1 receptor is upregulated. In addition, peptides may be preferentially released, at least in some systems (eg, SP/NK-1 receptor), when neurons or nonneuron cells are strongly activated and/or under pathological conditions.[41] Thus, NK-1 receptor antagonists (eg, nonpeptide NK-1 receptor antagonists) normally have no effect and will only act on deranged systems with increased peptide (eg, SP) release.

It is known that the NK-1 receptor is involved in the viability of tumor cells.[8] Following the administration of the siRNA *TACR1* (tachykinin 1 receptor gene) to cultured tumor cells, more apoptotic cells were found in siRNA cells than in cells not transfected and hence the number of siRNA tumor cells was significantly decreased in comparison with the number of nontransfected cells.[8] This is very important, because it is known that tumor cells develop strategies to neutralize the multiple pathways leading to cell death, and it seems that one of the most important of these strategies is the overexpression of the NK-1 receptor.[8] Tumor cells are highly dependent on the SP stimulus and the absence of the mitotic signal when the receptor is blocked with NK-1 receptor antagonists could tilt the balance within the cell to favoring apoptotic/death signals, and hence the cell dies.[8] [Figure 3b]. Thus, both pharmacological and genetic (siRNA) treatments induce the death of tumor cells by apoptosis. For this reason, the NK-1 receptor could be the Achilles' heel of cancer.

Nonpeptide NK-1 receptor antagonists could be considered a new generation of broad spectrum antitumor drugs.[7,8] For example, the antitumor action of aprepitant against GI cancer cells (pancreatic cancer, gastric and colon cancer, and hepatoblastoma) has been reported. Aprepitant inhibits 100% of GI cancer cells in a concentration-dependent manner; pancreatic cancer, gastric and colon cancer, and hepatoblastoma cells die by apoptosis[5,7,27] [Table 2]. The NK-1 receptor antagonist L-733,060 exerts an antitumor action *in vitro* and *in vivo* against cholangiocarcinoma[6] [Table 2]. The mechanisms of action of NK-1 receptor antagonists against cancer cells are multiple: They exert an antiproliferative action, induce tumor cell death by apoptosis, have antiangiogenesis effects, and inhibit the migration of tumor cells (they prevent invasion and metastasis)[3-5,7,8,30] [Figures 2b, d and 3b].

NK-1 receptor antagonists in combination therapy with cytostatic drugs have a synergic effect.[5] These antagonists decrease the side effects of cytostatics and radiation therapy.[42,43] Nonpeptide NK-1 receptor antagonists decrease the permeability of the brain–blood barrier (BBB) and hence can prevent metastasis[44] [Table 3]. The lipophilic nature of nonpeptide NK-1 receptor antagonists allow them to diffuse across the BBB and hence they could be used to treat brain metastasis.[45]

Nonpeptide NK-1 receptor antagonists could prevent GI cancer because they counteract chronic inflammation, which is a major risk factor for the development of GI cancer, and they could be also used for the treatment of GI cancer [Table 3 and Figure 3b]. Chronic inflammation is independent of the origin of chronic pancreatitis, hepatitis, and ulcerative colitis. In both chronic pancreatitis and ulcerative colitis and GI cancer the NK-1 receptor is overexpressed [Table 1]. It has been reported in a rat model of colitis-associated colon cancer that the animals treated with a NK-1 receptor antagonist had significantly reduced macroscopic and microscopic damage and a decreased incidence of inflammatory bowel disease. Twice as many of these animals had a normal diagnosis in all regions of the colon. A decrease in the proliferation index, Cox-2 expression, and active ERK1/2 was found in comparison with the vehicle-treated group. In Caco-2 cells, ERK1/2 was activated by SP and prostaglandin E2. Thus, NK-1 receptor antagonists may delay the development of further colonic damage, offering a potential treatment for patients with long-standing colitis.[46] NK-1 receptor antagonists exert a dual hepatoprotective and anti-inflammatory effect [Table 3]. Thus, nonpeptide NK-1 receptor antagonists (eg, aprepitant) could be useful for the prevention/treatment of GI cancer and hence the NK-1 receptor could be a new promising therapeutic target in GI cancer [Table 2].

CONCLUSION

NK-1 receptor antagonists could be considered as a new generation of antitumor drugs against GI cancer. The NK-1 receptor could be a specific molecular target for the treatment of cancer, since tumor cells upregulate and overexpress the NK-1 receptor [Table 1 and Figure 1a, b]. This could be an excellent new approach for the treatment of cancer (using NK-1 receptor antagonists). NK-1 receptor antagonists are broad-spectrum antitumor drugs [Table 2]. The mechanism of action is multiple: They exert an antiproliferative action against tumor cells; tumor cells die by apoptosis [Figure 2b and d]; they counteract the Warburg effect in tumor cells; they have an antiangiogenesis action, and they inhibit the migration of tumor cells, preventing invasion and metastasis [Figure 3b]. NK-1 receptor antagonists decrease the permeability of the BBB in the central nervous system and they could prevent brain metastasis. NK-1 receptor antagonists are safe and selective against tumor cells (the opposite of what happens with cytostatic drugs) [Table 3]. NK-1 receptor antagonists have synergic effects in combination therapy with chemotherapy and they decrease the side effects of cytostatics and radiation therapy. It is crucial to test the antitumor action of NK-1 receptor antagonists (eg, aprepitant) against GI cancer in human clinical trials. Aprepitant [Table 2] is a good candidate for testing its antitumor activity in future human trials, because the drug is currently used in clinical practice for the treatment of emesis and hence the required safety for this drug has already been carried out. It seems that by increasing the number of days on which aprepitant is currently administered in clinical practice (three days), and using higher doses (because tumor cells overexpress the NK-1 receptor) than those used for chemotherapy-induced nausea and vomiting, aprepitant could be effective in the treatment of GI cancer.

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Conflicts of interest

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