Substance P/Neurokinin 1 Receptor Involvement in Breast Cancer Progression Supports Therapeutic Repurposing of the Drug Aprepitant

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Received 09 September 2025; Accepted 05 November 2025

Abstract

This opinion article discusses the findings of a published article, which reported on the mechanism by which neuronal substance P (SP) drives metastasis through an extracellular RNA–TLR7 axis [1]. The role of SP in cancer is not a novel finding. Rather, SP's effect on cancer is linked to a long-held view on the neural–hematopoietic axis. Since the article omitted several

International Journal of Translational Science, Vol. 2, 153–164.
doi: 10.13052/ijts2246-8765.2025.023

seminal findings, we organized this review/commentary that discusses the landscape of SP in breast cancer. We also include our collective thoughts on the cited article that mostly support the past literature. Our article is intended to enhance the field of the neural-substance P-cancer axis and applaud the authors for their exciting findings. We believe that their findings further underscore the need to target breast cancer with an SP receptor antagonist. In this regard, we propose repurposing of aprepitant to treat breast cancer.

Keywords: .

Introduction

Cancer remains a major clinical issue, partly due to a high incidence of recurrence and drug resistance. Substance P (SP), a conserved neuronal peptide, is highly expressed in breast cancer (BC), resulting in autocrine and paracrine activation of the cancer cells and surrounding microenvironmental cells. This central role of SP within the tumor microenvironment has been supported by Padmanabhan *et al.* [1]. These interesting studies, along with similar studies by our group, indicated strong support for targeting the SP/Neurokinin-1 receptor (NK-1R) system. We discussed the potential of repurposing aprepitant, an FDA approved drug for chemotherapy-induced nausea and vomiting, to treat BC.

A recent report showed neuronal SP mediating metastasis in BC through the release of an extracellular RNA/TLR7 axis [1]. The authors reported on increased SP from the dorsal root ganglia (DRG). Further, they showed that this increase in SP was responsible for BC metastasis. Importantly, condition medium (CM) from 67NR tumor-DRG co-cultures (DRG-CM) contained higher levels of SP than tumor-CM (control). Tac1 $-/-$ DRG neurons had no impact on the invasiveness of 67NR spheroids, demonstrating that SP was required for the pro-invasive effects of DRG neurons on BC cells [1]. This is in line with other studies showing decreased production of SP in non-metastatic BC cell lines [2]. As per the description of 67NR, this cell line is non-metastatic. Thus far, this finding supports the long-held view of neuronal SP and non-neuronal SP in cancer behavior. However, the findings differ from other studies, which is addressed in the next paragraph.

Other studies showed SP inducing its own receptor, NK-1R on BC cells with a central regulatory role for cytokines [2–5]. The studies by Padmanabhan *et al.* suggested SP from sensory induced cell death of a small population of BC cells. The authors showed that this small subset of dying cells released

single stranded RNA (ssRNA), which activated the Toll receptor on other breast cancer cells to enhance BC metastasis [1]. Specifically, the ssRNA stimulated the BC cells in a paracrine manner by interacting with tumoral TLR7 receptors to drive BC growth and metastasis [1]. This actual report of a small population of BC cells expressing NK-1R contradicts several findings that showed increased NK-1R on cancer cells (discussed below).

It is important to highlight that the anti-emetic drug and NK-1R antagonist aprepitant was able to inhibit BC growth and metastatic progression of triple-negative BC (TNBC) in wild-type and immune deficient mice [1]. Importantly, the results by Padmanabhan *et al.* indicated that SP acted on NK receptors to induce cell death (apoptosis) when a small population of BC cells expressed high NK1 receptors. We and others reported on opposite effects.

SP may have multi-faceted roles, depending on the culture condition. As an example, SP was shown to mediate cancer cell survival in 2D cell cultures, while the opposite was seen using 67NR spheroids. The survival of spheroids most likely recapitulated an *in vivo* setting. More importantly, the survival of spheroids with SP suggested a survival benefit of cancer stem cells that are known to form spheroids [6]. Apoptosis is a double edged sword, with positive and negative outcomes for cancer. Specifically, the report on BC indicated that the more aggressive tumors have higher rates of apoptosis [7]. The negative effect is the survival of cells with a more primitive phenotype such as cancer stem cells. This latter effect could benefit long-term dormancy [8].

Padmanabhan *et al.* showed an indirect correlation between invasiveness and apoptosis [1]. This suggested that apoptosis was not a beneficial manifestation in BC. The studies however indicated that spheroids and other 3D settings closer to the *in vivo* setting should be harnessed to develop effective treatments. Therefore, although our studies may be different with respect to apoptosis, we are still in synergy with the findings on invasiveness and proliferation that are considered important pro-tumorigenic factors [2, 9]. Most importantly, the authors of the discussed article showed that aprepitant, an NK-1R antagonist, decreased tumor volume, which completely aligned with our studies [2, 9].

NK-1R is expressed on the membrane and within the cytoplasm of BC cells [9]. SP, which is released by BC cells, is also predominantly localized in the nuclei of BC cells [9]. The released SP can interact with other cells within the tumor microenvironment, and at distant sites. Macrophages and plasma cells at the peritumoral sites expressed NK-1R, suggesting that these cells could be activated by tumoral SP. This neuropeptide could also support

tumor through its angiogenic function. This function is indicated by the identification of SP in the nuclei of smooth-muscle and endothelial cells of small- and medium-sized blood vessels [9]. In addition to tumoral SP, BC can be supported by SP from neural sources [1, 9]. Thus, BC most likely has two control systems – an intrinsic or tumoral SP mediated by BC cells and the microenvironment (endothelial cells and inflammatory cells), and an extrinsic or neuronal SP mediated by fibers [9].

Intrinsic SP could maintain a network to support the tumor through autocrine, paracrine, intracrine and endocrine stimulation. Autocrine stimulation occurs with BC-derived SP interacting with NK-1R on the BC cells to mediate mitogenesis. Paracrine stimulation occurs when SP released from BC cells interacts with NK-1R on other BC cells, and on cells within the tissue microenvironment. Intracrine stimulation occurs when cytosolic SP migrates to the nuclei to regulate nuclear functions in BC cells. Endocrine activation could occur with BC-derived SP in the circulation to enhance distant metastasis [5]. This latter function is supported by studies reporting higher plasma levels of SP in BC patients relative to healthy subjects [10]. Furthermore, SP could evade degradation by interacting with circulating fibronectin to allow for distant function [11].

We have previously demonstrated SP as a universal mitogen in all human cancer cells studied and NK1-R antagonists blunt cancer cell proliferation [12]. SP activated NK-1R on cancer cells to induce tumor-cell mitogenesis by activating mitogen-activated protein kinases (MAPKs), c-Myc, AP-1 and NF-κB [12]. SP can also mediate tumor cell proliferation, migration and invasion by upregulating the expression of Toll-like receptor-4 (TLR-4) in tumor cells [12, 13]. In contrast, specific NK-1R antagonists, including aprepitant, counteracted all these effects.

It is worthwhile highlighting the possible risk factor role that persistent pain could play in BC. Specifically, 90% of subjects with BC, particularly TNBC, succumb to metastatic disease and severe pain [14]. Overall, in addition to aprepitant targeting BC cells, it could be important to mitigate pain associated with SP [9, 12–14].

Regarding the safety of aprepitant, the IC50 of aprepitant for human breast epithelial cells was three times higher than BC cells [9]. More importantly, NK-1R is essential for the viability of cancer cells with no effect on normal cells [15]. Aprepitant can prevent brain metastases by decreasing the permeability of the blood–brain barrier [12]. Thus, aprepitant can blunt further brain metastasis while allowing for treatment of residual cancer cells within the brain; a patient with brain metastases from BC was treated with

aprepitant 80 mg/day and subsequently 125 mg/3 days for 6 months. This treatment resulted in clinical improvement and decreased tumor-biomarker CA153 [16]. Similarly, in a lung-cancer patient treated with aprepitant (1,140 mg/day; 45 days) and radiotherapy, the lung-tumor mass disappeared with no side effects [17]. A recent study, reported that aprepitant given during chemotherapy showed lower risk of cancer recurrence with better survival in TNBC [18].

An effective antitumor effect could be achieved with aprepitant by assessing the current dose used/time administered in clinical practice [12, 19]. Furthermore, aprepitant could be used to circumvent the serious side effects of chemotherapy and radiotherapy [20]. A justification of this statement is based on our unpublished preclinical murine studies with triple negative MDA-MB 231 BC cells. These studies support repurposing of aprepitant to achieve both anti-tumor and cardioprotective effects in response to doxorubicin.

Thus far, as far as we are aware, there are no FDA approved peptide receptor antagonists for BC. Given these facts, combined with the following information, (a) a SP/NK-1R system highlighted in a recently published article as the most widely studied peptidergic system in cancer [1]; (b) the safety profile of aprepitant; (c) the numerous preclinical and clinical evidence of its antitumor activity in cancer, we propose that aprepitant should be repurposed to treat BC – metastatic and dormant. We envision treatment in combination with chemotherapy or radiotherapy for BC patients. Furthermore, we suggest that phase I clinical trials are needed to evaluate the safety of aprepitant at higher doses, and phase II trials to evaluate its efficacy in combination with chemotherapy or radiotherapy are urgently needed in BC patients.

This review/commentary arises after communication with five different worldwide laboratories engaged in SP/NK-1R research. The seminal studies conducted by the authors of this opinion, along with the discussed article, serve to alert the scientific community and the pharmaceutical industry to take note of the importance of the SP/NK-1R system in cancer [1]. It is important to acknowledge an urgent need for repurposing aprepitant as an anti-tumor drug in BC.

Response to Article (1)

The authors within the introduction dedicated three citations pertaining to glioma cells forming functional synapses with neurons to promote tumor growth and invasion. We were surprised that the authors omitted a very important article directly pertaining to SP, NK-1R and NK-1R antagonists

in BC [9]. The corresponding authors attributed this to limitation of citations by the journal (communication with Dr. Munoz).

Regarding Figure 1I, the authors attributed the effects of capsaicin treatment in the reduction of BC volumes as follows: (a) capsaicin induced, sensory-specific denervation of tumors; (b) capsaicin being a TRPV1 agonist and neurotoxin that degenerates sensory nerves being responsible for decrease in tumor volume. The authors did not address the possibility of SP depletion as the cause. Capsaicin, the active component in chili peppers, triggers the release of SP from nerve endings to induce pain and inflammation. Prolonged exposure to capsaicin can deplete these nerve endings of SP, potentially leading to reduced pain perception. SP is widely known for its tumorigenic potential in a multitude of cancers shown by our group for BC and other cancers. The authors failed to discuss the possibility that depletion of tumorigenic SP to reduce tumor growth after capsaicin treatment. In fact, they needed to eliminate the possibility of SP being the cause by injecting SP daily, or twice/thrice a day in the 4T1 injected animals. This would be able to determine if SP increases tumorigenicity *in vivo* rather than relying on *in vitro* models which do not necessarily recapitulate *in vivo* condition.

In Extended Data Figure 2b, the authors stated that cancer cells can migrate along nerves through a process of perineural invasion, requiring physical contact. The authors did not observe physical interactions between neurons and cancer cells (Extended Data Figure 2b). Based on this, they hypothesized that DRG neurons may mediate pro-metastatic effects by secreted molecules. Despite several articles on mitochondrial transfer by tunnelling nanotubules, the authors omitted this possibility of BC-neuronal communication [21, 22]. Although the authors stated that they did not detect physical interactions between neurons and cancer cells, enlarging the image in Extended Data Figure 2b showed evidence of a thin tunnelling nanotubes.

The authors indicated that only a small population of BC cells express NK-1R and this subset was killed by SP. We and others in the field have demonstrated and reported on the increased NK-1R on the majority of BC cells, relative to non-tumorigenic cells. Furthermore, the authors highlighted the importance of single-stranded RNA (ssRNA) over SP in mediating tumorigenic effects. More importantly, the authors stated that the use of RNases specific for ssRNA (RNase T1) or double stranded RNA (dsRNA, RNase III), implicated ssRNAs as mediators of the pro-invasive effects of DRG effects on BCCs (Figure 3c, Extended Data Figure 7f). It is nuclear if

the authors claim an independent method of ssRNA in the pro-invasive effects of DRG.

ssRNA plays a crucial role in the expression of the preprotachykinin gene, which encodes the neuropeptides SP and neurokinin A (see graphical abstract). Specifically, messenger RNA (mRNA), a type of ssRNA, carries the genetic information from the preprotachykinin gene to the ribosomes, where proteins are synthesized. Therefore, it may very well be possible that mRNA associated with the preprotachykinin gene may be targeted by the RNase T1, as indicated in the author's publication. Hence, ultimately it amounts to preprotachykinin gene-derived SP that might be the pro-invasive mediator and not necessarily the ssRNAs alone. Based on this argument, the findings by the authors add to the complex network of SP.

It should be noted that alternative splicing of the preprotachykinin transcript could lead to the production of various tachykinin peptides. Seminal findings showed tissue-specific generation of two preprotachykinin mRNAs from one gene by alternative RNA splicing [23]. This article clearly demonstrated that alternative RNA splicing generates two distinct mRNAs encoding the neuropeptide SP alone or with substance K from a single preprotachykinin gene. Alternative splicing of the preprotachykinin mRNA is a key regulatory mechanism that determines the type of peptides that are produced from a single gene. For example, the Tac1 gene produces at least four different mRNA variants (alpha, beta, gamma, and delta) through alternative splicing. These variants differ with respect to exon contents and this determines the final tachykinin peptides generated. Some examples of ssRNA (mRNA) variants for preprotachykinin include:

Alpha-PPT mRNA: Lacks exon 6 and primarily encodes SP.

Beta-PPT mRNA: Contains all seven exons of the gene and encodes SP, Neurokinin A, and Neuropeptide K.

Gamma-PPT mRNA: Lacks exon 4 and encodes SP, Neurokinin A, and Neuropeptide Gamma.

Delta-PPT mRNA: Lacks both exons 4 and 6, and only encodes SP.

These mRNA variants, all single-stranded RNA molecules, are translated into distinct tachykinin peptides for post-translational processing to produce the final tachykinin peptides. This process highlights the crucial role of alternative RNA splicing in regulating the expression and diversity of neuropeptides from a single gene. Therefore, it may be possible that one or more of these mRNA variants are translated into preprotachykinin proteins

and processed to tachykinin peptide, more specifically SP. This explains the pro-tumorigenic effects reported as ssRNA.

Importantly, the authors observed that treatment of 67NR spheroids with SP in the presence of RNase A, which completely abolished the invasion-promoting effects of SP (Figure 3d). Two very important points need to be addressed on this finding: (1) the studies lack a critical control with SP in the absence of RNAase; (2) SP is an 11 amino acid peptide that is rapidly degraded *in vitro*. Although the NK-1R could be desensitized by re-adding SP, this experiment could be done to determine there was a need to ensure that SP was retained in the culture.

Treatment with ssRNA40 significantly increased spheroid invasion and proliferation (Figure 3e; Extended Data Figure 7 g, h). In this set of studies, the authors do not take into consideration, nor have they shown that addition of, the ssRNA of the preprotachykinin gene may simulate their findings.

The authors stated that neuronal SP could induce ssRNA release by cancer cells either *via* a regulated secretory pathway or by cell death. The authors identified a small ($<1\%$ of spheroid area) but significant increase in cancer cell apoptosis upon co-culture with neurons or treatment with SP (Figure 3h). An explanation for this finding could be as follows: SP induced different effects in multiple cell types. SP is known to be a universal mitogen in cancer cells [19]. Furthermore, SP is not toxic to fibroblasts, even at millimolar concentrations. Importantly, nanomolar concentrations of SP were observed to be neurotoxic in primary cultures of striatal, cortical and hippocampal neurons, inducing delayed cell death [24]. All three types of neurons were sensitive to micromolar concentrations of SP after 48 h exposure, and to nanomolar concentrations at 7 day exposure. Likewise, SP can induce apoptotic effects in DRG neurons. Therefore, it is possible that the apoptosis observed by authors in 67NR spheroids and DRG neuron co-cultures treated with SP did not originate in BC cells, but rather in DRG neurons. It is well known that NK-1R is highly expressed in neurons [25]. To add credence to the above statement is the fact that dying cells (in this case neurons) can express and release death ligands (e.g., Fas Ligand, TNF-α, TRAIL). These ligands bind to specific death receptors (e.g., Fas, TNFR1, TRAILR1, TRAILR2) on the surface of neighboring cells. This binding could trigger the extrinsic apoptosis pathway in those neighboring cells. The death receptors then recruit adaptor proteins and initiate a series of events leading to caspase activation and, ultimately, apoptosis. Furthermore, dying cells can also release signals that are internalized by neighboring cells, potentially affecting their apoptotic pathways. These may include:

(a) mitochondrial factors: factors released from the mitochondria of dying cells (e.g., cytochrome c, AIF, Smac/DIABLO) that could potentially transfer to neighboring cells and trigger the intrinsic apoptosis pathway. (b) Apoptotic cells can release exosomes, containing various molecules like proteins, DNA and RNA that can carry pro-apoptotic signals to recipient cells, influencing their apoptotic activity. In conclusion, the apoptosis in 67NR spheroids and DRG neurons co-cultures treated with SP probably originated upon *in vitro* co-culture of spheroids with DRG neurons, due to the above factors.

Competing interest statement: The authors declare no competing financial and/or non-financial interests in relation to the work described.

Author contributions statement: All authors have made substantial contributions to the conception/design and all have contributed to drafting the document.

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