Review Article
Running Title: Targeting NK1R System in Breast Cancer Treatment
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A Narrative Review on Targeting Neurokinin-1 Receptor (NK1R) System: A New Strategy for Breast Cancer Treatment

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Abstract
Breast cancer is among the leading causes of cancer-related death worldwide, with its incidence steadily increasing. While multiple factors contribute to its development, understanding the interplay of molecular and cellular pathways is essential for effective therapeutic strategies. Among these, the tachykinin family—particularly the neurokinin-1 receptor (NK1R)—has emerged as a significant player in breast cancer progression. Substance P, a key agonist of NK1R, and the proliferative marker Ki-67, have both been implicated in tumor development. The purpose of this narrative review was to examine recent findings suggesting that NK1R antagonists not only exert antiproliferative and antitumor effects but may also mitigate chemotherapy-induced side effects, such as nausea. These observations clarify existing gaps related to the connection between NK1R, substance P, and Ki-67, and the level of confidence in the drug efficacy of breast cancer.

Keywords: Breast neoplasms, Neurokinin-1 receptor (NK1R), Substance P, Ki-67, Targeted therapy

Introduction

Breast cancer (BC) is an important public health problem that plagues the world. A total number of 2,296,840 novel cases and 666,103 deaths in 2024 alone reveal the exerting influence of cancer. The incidence and mortality percentage for Asia, which makes BC the fourth most common female cause of cancer mortality, are 42.9% and 47.3%, respectively.[1] In men, the occurrence is uncommon, below 1 per 100,000 person-years.[2] Women > 50 years carry a disproportionate burden of the disease,

accounting for over 70% of new cases and 81% of BC deaths. Based on recent projections, the incidence of new cases is projected to increase to 3 million new cases per year in 2040 worldwide, and cancer deaths are projected to reach 1 million per year.[3]

BC is a heterogeneous malignancy, which is categorized into 4 broad molecular subtypes based on the expression of the progesterone receptor (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2): Luminal B, HER2-positive, Luminal A, and triple-negative breast cancer (TNBC).[4] They demonstrate varied clinical behavior, prognosis, and response to treatment and require individualized treatment regimens.

Present methods of treatment for BC are surgery, radiation therapy, chemotherapy, hormone (endocrine) treatment, immunotherapy, and targeted therapies. Surgery is mostly the resection of the tumor and involved lymph nodes. Radiotherapy is the use of high-energy waves to kill remaining cancer cells, either external beam or internal.[5] Chemotherapy with the use of cytotoxic agents like paclitaxel, docetaxel, epirubicin, and capecitabine is used to shrink the tumor size, decrease the likelihood of recurrence, and relieve symptoms in later stages.[6] Hormone therapy is accomplished through blocking hormone production or preventing hormone-receptor interaction in hormone-sensitive cancers. Immunotherapy and targeted therapy are more recently developed ideas, which kill cancer selectively but do not cause extensive harm to normal tissues.[5]

While chemotherapy and radiotherapy continue to be the conventional modes of treatment, their acute and chronic toxicities and side-effects have generated some interest in new target-based strategies with greater efficacy and fewer side-effects. Recent research has focused on the tachykinin family, specifically substance P (SP) and its most significant receptor, neurokinin-1 receptor (NK1R), as prime actors in BC pathophysiology. The family of tachykinins comprises SP, neurokinin A (NKA), and neurokinin B (NKB), which affect certain G protein-coupled receptors (NK1R, neurokinin-2 receptor (NK2R), and neurokinin-3 receptor (NK3R), respectively). SP is the most widespread and biologically active tachykinin, secreted mainly in the peripheral and central nervous system and immune cells.[7] SP is involved in pathological and physiological processes such as the transmission of pain, vasodilation, wound repair, and significant cancer development. SP possesses a very high binding affinity for NK1R, which exists in two isoforms—truncated (NK1R-Tr) and full-length (NK1R-FL). Both these isoforms are co-expressed in BC tissues and were shown to participate in cell growth and tumor development.[8]

It appears that this disease is characterized by significant alterations in protein expression within cancerous tissues, with the majority of affected proteins showing reduced or absent expression, highlighting their potential utility as biomarkers for diagnosis and therapeutic targeting.[9] Several studies have examined the relationship between the expression of SP and NK1R, but this connection remains unclear in hormone receptor (HR)-positive tumors. In addition, the connection between NK1R with Ki-67, the overall survival rate, and HER2 needs further investigation with a larger sample size. Different studies have reported some inhibitory effects of NK1R or NK2R antagonists, and scientists have found that the phenotype of cytostatic tumors must be determined to reach the best result for cancer treatment. Thus, additional studies are needed to specify the use of these anti-cancer drugs for every patient with a different prognosis.

The second important marker that plays a role in the biology of BC is Ki-67, a nuclear protein characterized by cell proliferation correlation. It is found in all phases of the proliferating cell cycle (G1, G2, M, and S) and not found in resting cells (G0), thereby making it an effective biomarker for tumor grading and prognosis.[10] Strong Ki-67 expression levels are associated with malignant tumor aggressiveness and unfavorable clinical courses. Suggestive evidence of NK1R expression and Ki-67 association has also been found in various cancers, including BC.[11] In preclinical models, NK1R inhibition was found to significantly suppress Ki-67 expression, thereby establishing its function in tumor growth. Concurrently, dysregulation of FOXA1, RMRP, and NEAT1—identified as key upregulated genes in metastatic breast tumors—further underscores the molecular complexity of BC progression and highlights their potential as complementary diagnostic or prognostic biomarkers.[12] Because of the high frequency of BC and the limitations of traditional therapies, targeted treatment on molecular signal pathways has been of special interest in recent research. The present review outlines the SP/NK1R system and its function in Ki-67 BC development, with regard to its value as a new therapeutic target for more successful treatment with fewer side-effects.

Overview of BC

BC is categorized into some groups based on histological, molecular, and cellular investigations. According to an original research study conducted by Mehmet Furkan Sağdıç, et al., in 2025, rare BC types in terms of histology are tubular carcinoma, apocrine carcinoma, secretory carcinoma, micropapillary carcinoma,[13] and the common ones in terms of molecular classification are Luminal B, Luminal A, HER2-positive, and TNBC.[4]

Some therapeutic approaches have been detected, most of which have a profound effect on the amelioration of cancer. There are some molecular factors that anticancer drugs can target to prevent the cancer from getting worse, such as NK1R, SP, Ki-67, ER, PR, and HER2.

A research study conducted by Mahas Al-Keilani, et al. in 2023 has shown that SP is connected with aggressive tumors, while it is not related to the size and grade of tumors, the expression of Ki-67, and it also does not have a connection with the expression of HER2 in patients with HR-negative. However, it is positively related to HER2 in patients with HR-positive (P = 0.001).[11] Another study has concluded that the high production level of Ki-67 is related to ER-negative and PR-negative, which shows the characteristics of the TNBC subtype. Also, it has relatively high expression in HER2-enriched, anda positive connection with HER2.[14] A recent research study has demonstrated that the NK1R expression has positively correlated with the expression of Ki-67 (P = 0.012),[15] and the expression of SP in patients with HR-negative (P = 0.01),[14] and it is not related to ER, PR, and HER2. The production of NK1R is high in aggressive tumors.[15] As a result, the high expression of NK1R, SP, and Ki-67 exists in tumors with a poor prognosis. The following is a summary of characteristics of common BC subtypes.

Luminal A

Characterized by ER+ / PR+, non-expression of HER2, and low Ki-67 rate (<20%). The subtype is prognostically favorable, has low recurrence risk, and high survival.[4] Patients having Luminal A tumors will have a good response to endocrine therapy and little response to chemotherapy.[16] The overall survival was 95.5%, and the rates of local and regional recurrence were 1.5% and 0.7%, respectively.[17]

Luminal B

Luminal B BC is characterized as ER+ and either PR+ or PR-, HER2 status positive or negative, and separated by high expression of Ki-67 (>20%).[4] It also represents 10%-20% of BC and is of worse prognosis than Luminal A.[18] They are treated with a mixture of hormone therapy and chemotherapy. Survival rate is approximately 90%, local recurrence of 2.9%, and regional recurrence of 1.5%.[17]

HER2-positive

Representing 10%-15% of BC, this subtype is further classified into luminal/HER2 (PR+, ER+, HER2+, any Ki-67) and HER2-enriched (ER-, HER2+, PR-).[19] Management may include HER2-targeting drugs like trastuzumab and pertuzumab, together with chemotherapy. Endocrine treatment can be useful in the case of luminal HER2 patients.[20] The reported survival rate for luminal/HER2 is 85.7%, and for HER2-enriched is 79.8%. The regional recurrence rate for luminal/HER2 is 2.2%, and for HER2-enriched is 4.9%. Also, the local recurrence rate is 3.4% for luminal/HER2 and 7.5% for HER2-enriched.[17]

TNBC

This subtype does not express PR, ER, or HER2 and accounts for 10%-20% of BC. TNBC is the poorest type with an unfavorable prognosis and scant targeted therapy.[21] Chemotherapy is still the most commonly used treatment option owing to the lack of targetable markers.[22] TNBC has a survival rate of 80.9%, and 7.6% (local) and 3.3% (regional) rates of recurrence.[17]

In spite of the existence of several treatment modalities, traditional therapies like radiotherapy and chemotherapy will tend to yield debilitating side effects that erode quality of life. These drawbacks reinforce the need for new therapeutic methods. This review notably singles out the NK1R pathway as a useful molecular target in the treatment of BC, a promising opportunity with fewer side-effects.

NK1R and Its Interaction with Molecular Pathways

NK1R

The neurokinin receptor family (NK1R, NK3R, and NK2R) belongs to the G protein-coupled receptor (GPCR) family with 7 transmembrane domains. Of these, NK1R has the broadest expression in human tissues and the highest affinity for SP.[9] While NKA and NKB are bound by NK1R, their affinities are considerably lower than that of SP.

SP–NK1R signaling has been implicated in many pathological and physiological processes, such as depression,[23] neurogenic inflammation, pain, wound healing, and cardiovascular diseases.[8] NK1R antagonists netupitant and aprepitant are used for treating chemotherapy-related nausea and vomiting (CINV).[24]

NK1R is encoded by the chromosome 2 gene TACR1. NK1R possesses seven hydrophobic transmembrane domains, three extracellular and three intracellular loops.[9] Two isoforms of significant size are NK1R-FL with 407 amino acids and NK1R-Tr with 311 amino acids. Highly expressed in non-tumorigenic tissue, like the brain and normal breast epithelium, NK1R-FL was shown to be growth inhibitory to a tumor. The NK1R-Tr is overexpressed in cancerous breast tumors, and involved in the induction of DNA synthesis and oncogenic pathway activation, like epidermal growth factor receptor (EGFR) and mitogen-activated protein kinase (MAPK).[25, 26]

Structurally and functionally, these two isoforms are vastly different. NK1R-Tr does not possess the entire C-terminal domain required for β-arrestin binding, which is detrimental to the receptor desensitization and internalization. This makes NK1R-Tr cause prolonged activation of extracellular signal-regulated kinases1/2 (ERK1/2), promoting proliferative and anti-apoptotic action. NK1R-FL, however, has stronger binding to SP and acts more efficiently with

β-arrestin, thereby leading to quicker but better-modulated ERK signaling.[27]

SP

SP belongs to the tachykinin neuropeptide family and is released in immunocompetent cells (e.g., dendritic cells, eosinophils, T cells) and neural and epithelial cells. SP is encoded by the TAC1 gene found on chromosome 7, with other peptides such as NKA and neuropeptide K (NPK). SP contains 11 amino acids and amphiphilic characteristics. Its C-terminus is hydrophobic and interacts with the lipid bilayer of cell membranes, and the N-terminus is polar and permits diversified functional activities.[8, 28]

SP is most attracted to NK1R among neurokinin receptors. On this binding, SP is held responsible for transmitting several physiological as well as pathological effects, such as inflammation, angiogenesis, carcinogenesis, and immunomodulation.[8] Of specific note, SP–NK1R binding triggers the recruitment of GPCR kinases (GRKs) and β-arrestin, which, in a complex, regulate downstream responses dependent on SP concentration. When SP is high (>10 nM), this signaling is sustained, leading to lysosomal degradation of NK1R. After β-arrestin release, SP is degraded by endothelin-converting enzyme 1 (ECE1) before recycling of NK1R.[29]

Ki-67

Ki-67, a nuclear protein and a principal cell proliferation marker, is located on chromosome 10. Ki-67 is present in all stages of the cycling cell's active phase—G1, G2, S, and M—and not in resting G0-phase cells.[30]

There are several studies that have shown a robust association of NK1R expression and Ki-67 levels in cancers like BC,[31] oral squamous cell carcinoma,[32] and odontogenic tumors.[33] Elevated Ki-67 expression is associated with a bad prognosis, higher tumor aggressiveness, and low survival rates.[31]

Since it plays a pivotal position in tumor biology, Ki-67 is not only a prognostic factor but also a potential target for therapy.[30] In normal breast tissue, Ki-67 positivity is <3%, whereas in malignant tissue, the positivity is markedly high, which establishes the evidence for a high proliferative index and unfavorable clinical behavior.[34]

In recent decades, scientists have detected some Ki-67 antibodies, such as MIB-1-using chromogenic detection and immunofluorescent labeled (MIB1-IF), B65, Poly, 30-9, SP-6. An original research study conducted by Balazs Acs, et al., in 2017, has concluded that in cases where the cut-off of Ki-67 in BCs is 20%, all antibodies except MIB-1-IF will divide patients into two groups of worse and better prognosis, and at a 30% cut-off, all of them except B65 and MIB1-IF successfully classified patients based on prognosis.[35]

Interaction of the SP/NK1R system with central BC pathways

BC progression is characterized by complex interactions among diverse molecular pathways. Cumulative evidence favors the view that the SP/NK1R axis, in addition to triggering signaling cascades that are directly involved in the proliferation of tumor cells, also indirectly facilitates invasion, inflammation, immune escape, metastasis, and drug resistance by modulating central oncogenic pathways such as MAPK, Wnt/β-catenin, Transforming Growth Factor Beta (TGF-β), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), EGFR, and PI3K/Akt. The schematic figure of these molecular pathways related to BC is shown in Figure 1.

In-vitro studies employing MCF-7 cancer cells revealed that SP activation of NK1R was coupled with NF-κB activation, the key regulator of inflammation, cell survival, and migration. Jafari Nezhad et al. showed that the activation of SP produced higher levels of Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), reactive oxygen species (ROS) production, and NF-κB

mRNA expression.[36] Excessive ROS is the underlying cause of overexpression of inflammatory mediators and induces genetic instability, an easy niche for cancer development. TNF-α also activates C-X-C chemokine receptor type 7 (CXCR7) to promote lymphatic migration of cancer cells.[37] It signals through tumor necrosis factor receptor 1 (TNFR1) and tumor necrosis factor receptor 2 (TNFR2), the latter of which induces tumor cell survival and immune evasion.[38] IL-6, in contrast, activates Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling, which leads to proliferative and anti-apoptotic genes like cyclin D1, c-Myc, and Bcl-2.[39, 40]

At the tumor-suppressor level, concentrations of SP as high as 400 nM caused the inhibition of p53 and p21 expression, both being key components in cell cycle arrest and DNA repair. This action demonstrates the ability of SP/NK1R signaling to bypass cellular defense and induce uncontrolled proliferation.[36]

The SP/NK1R system also interacts with the TGF-β system that has twofold roles in cancer. In early tumors, TGF-β is a tumor suppressor, but in cancer, it induces epithelial–mesenchymal transition, invasion, and metastasis. In HR+ BC, TGF-β induced upregulation of NK1R-Tr expression via the activation of Smad4, a transcriptional mediator that increases the expression of the NK1R-Tr gene.[41] NK1R-Tr then activates ERK1/2 and PI3K/Akt signaling to induce cell cycle progression (through cyclin D1 and cyclin B1) and survival.[41, 42]

Notably, Smad1 and Smad3 usually inhibit the TGF-β oncogenic signal, but the Wnt pathway can reverse them. The Wnt/β-catenin pathway activation stabilizes β-catenin and induces transcription of oncogenes c-Myc and cyclin D1, enhancing tumor malignancy.[41] Various reports presented that NK1R antagonists inhibit the activation of the Wnt pathway in cancers like hepatoblastoma and melanoma, and postulate an inhibitory role of NK1R on the Wnt signaling.[43, 44]

Another crucial pathway regulated by NK1R is the MAPK signaling pathway, such as ERK1/2 and p38 MAPK, related to proliferation, migration, and chemoresistance.[45] Li et al. demonstrated that SP promotes matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-14 (MMP-14) expressions, the key enzymes responsible for extracellular matrix degradation, by activating ERK1/2, c-Jun N-terminal kinase (JNK), and Akt. It was protein kinase A (PKA) and protein kinase C (PKC) mediated and finally triggered NF-κB and AP-1 transcriptional activity.[46] Furthermore, β-arrestin, a phosphorylation-binding NK1R, is capable of mediating long-term ERK1/2 activation and treatment resistance.[47]

TGF-β also has the capability to activate MAPKs through Smad-independent pathways. TGF-β is capable of initiating non-canonical signaling (e.g., ERK1/2, JNK, p38), tumor growth, and antiapoptosis in Smad4-deficient tumors.[48] This demonstrates how tumors are capable of diverting TGF-β signaling from suppression towards pro-oncogenic activity via NK1R and MAPK interaction.

EGFR transactivation is a second critical mechanism regulated by SP/NK1R. NK1R activation phosphorylates and activates EGFR, increasing downstream MAPK and PI3K/Akt signaling and promoting G1/S cell cycle progression.[45, 49, 50] NK1R overexpression in TNBC is responsible for maintaining EGFR-dependent tumor growth, and blockade of the receptor decreases invasiveness.[45, 51] SP-induced MMP activity also mediates EGFR ligand shedding that generates autocrine/paracrine feedback loops that sustain signaling.[52]

Furthermore, SP/NK1R signaling is also able to transactivate HER2 and confer drug resistance upon HER2+ BCs. This is c-Src–dependent and inhibited by the application of c-Src inhibitors (e.g., 4-(4'-phenoxyanilino)-6,7-dimethoxyquinazoline). The inhibition of c-Src, along with MMP inhibitors, significantly inhibited the survival and migration of HER2+ and EGFR+ BC cells.[53] The communication between SP/NK1R and these pathways demonstrates the pivotal role of this system as a signaling hub, integrating multiple oncogenic inputs and coordinating tumorigenic outputs such as growth, invasion, inflammation, and resistance.

Targeting the NK1R system in BC

The NK1R system, through its primary ligand SP, is among the major regulating systems of tumor cell growth, proliferation, metastasis, angiogenesis, and drug resistance to cell death. Its ubiquitous expression in human tissues, and especially its overexpression in the majority of cancers, has made NK1R a potential therapeutic molecular target for cancer. Recent research has demonstrated the therapeutic use of NK1R antagonists to be not just anti-tumor, but also to minimize the side-effects of conventional cancer therapy. The BC antagonists are tabulated in Table 1. Aprepitant, an NK1R antagonist approved for the treatment of CINV, exhibited remarkable antiproliferative action in the majority of cancer models, including BC.[54]

In models of hepatoblastoma, cell lines HepG2, HepT1, and HuH6 expressing predominantly NK1R-Tr were sensitive to NK1R antagonists L-733,060, L-732,138, and aprepitant. The treatment caused a regression of the tumor, reduced Ki-67 expression, and inhibited angiogenesis with no systemic toxicity.[55] This shows that NK1R antagonists act in the majority through NK1R-Tr, the isoform that is upregulated more often in cancer.

In addition, increased NK1R expression has been found in tumor tissues but not in the surrounding normal tissue in BC. Immunohistochemical analysis has shown NK1R to be expressed in the cytoplasm, membrane, and nucleus of the dominant tumor cells in most patients.[56] The overexpression of NK1R and SP in cancer has been associated with high Ki-67 indices and poor hormone receptor status, particularly in more aggressive forms such as TNBC.[15]

Experiments involving several BC cell lines, such as T47D, MCF-7, and MDA-MB231, have established the pro-apoptotic and antiproliferative nature of NK1R antagonists. They are implemented through the suppression of key survival cues like ERK1/2, PI3K/Akt, and NF-κB, and inhibition of MMP activity and migration/invasion-related genes.[57]

Several NK1R antagonists have been studied in preclinical models, and all of them have shown varying efficacy and mechanisms:

• L-732,138 / L-733,060: Traditional NK1R antagonists that reduced cell viability significantly and caused apoptosis in breast as well as liver cancer models.[55, 57]

• Aprepitant: Blocked tumor development in-vitro and in-vivo, although it is already Food and Drug Administration (FDA) approved for the purpose of CINV, thereby constituting a potential repurposing drug.[54]

• MEN 11467: The drug used as the NK1R antagonist in BC and suppressed the tumor proliferation for extended durations without being permanently cytotoxic in mice. The combination of MEN 11467, Nepadutant (MEN 11420, as an NK2R antagonist), and NKA (as an agonist) has a profound impact on the growth of tumors.[58]

• MEN 11149: Selective human NK1R antagonist that inhibited glioma cell growth, suggesting wider anticancer effects.[59]

• NKP 608: In colorectal cancer models, induced apoptosis through augmented

expression of caspase-3 and Bax and downregulated Bcl-2. Also, inhibited Wnt pathway targets (e.g., cyclin D1, VEGF) and re-expressed E-cadherin.[60]

• ASN-1377642: Targeted the MDA-MB-231 cell line's NK1R and suppressed growth (26).

• RP67580: Tested first in mice and rats, the drug was reported to affect ERK and Akt phosphorylation patterns without inhibiting p38 function.[61, 62]

• SR140333, C-99,994, CP-96345: In the T47D breast tumor cell line, these compounds were receptor-specifically inhibited, and the growth of tumor cells was reduced.[63, 64]

Besides monotherapy, combination therapy has also been reported to be synergistic. For instance:

• L-733,060 + vinblastine: Both of these, in combination, increased cytotoxicity by destabilizing microtubules and sensitizing the cancer cells to chemotherapy.[65, 66]

• NK1R antagonists + Cyclooxygenase-2 (COX-2) inhibitors: In the TNBC models, this combination inhibited both chemo-resistant tumor cells and cancer stem cells. Overexpression of SP, COX-2, and NK1R in TNBC renders this combination very effective.[67]

• NK1R antagonists + chemoradiotherapy: Concurrent administration suppressed treatment-evoked neurogenic inflammation in the gastrointestinal and urinary tracts without affecting antitumor activity.[68, 69]

These effects explain the dual therapeutic function of NK1R antagonists: not only are they inherently tumor cell survival and metastasis inhibitors, but they also are supportive drugs to counteract the side-effects of conventional treatments.

As they possess their known safety profile in the clinic (e.g., aprepitant), they have demonstrated effectiveness against diverse tumor models and possess a broad mechanism of action. NK1R antagonists are good targets to be further investigated for the treatment of BC. Their application, alone or in combination with other chemotherapeutic drugs, could emerge as a new mechanism to bypass drug resistance, lower side effects, and maximize patient benefits.

Conclusion

BC remains the most common and fatal cancer in the world, its TNBC type being the most lethal and treatment-resistant because it lacks ER, PR, and HER2 expression. Although traditional treatments like surgery, chemotherapy, and radiotherapy have optimized prognosis, their effectiveness is usually limited by systemic toxicity, drug resistance, and recurrence. Those limitations highlight the urgency even more to apply new therapy approaches that are effective and acceptable.

Preclinical and translational research have pointed to the NK1R system, through its ligand SP, as a possible therapeutic target in BC. The SP/NK1R signaling pathway is implicated in tumor cell proliferation, survival, angiogenesis, migration, immune evasion, and resistance to apoptosis—typical cancer hallmarks. Significantly, this pathway intersects with several oncogenic cascades such as PI3K/Akt, NF-κB, EGFR, MAPK, Wnt/β-catenin, and TGF-β, which makes NK1R an etiological convergence point in the case of BC.

Interestingly, NK1R antagonists like aprepitant, L-733,060, MEN 11467, and others have been demonstrated to exhibit significant antitumor activities in-vitro and in-vivo models. These agents inhibit Ki-67 expression, MMP activity, induce apoptosis, and inhibit tumor growth. In addition, combination therapy with anticancer drugs (e.g., vinblastine), COX-2 inhibitors, or pathway inhibitors of the HER2/EGFR pathway and NK1R antagonists has been shown to have synergistic effects on bulk tumor cells and resistant subpopulations, including cancer stem cells. Their additional capacity to inhibit inflammation caused by

chemotherapy and radiotherapy gives them a dual role as supportive and curative therapy.
Although current evidence is strong, the majority of the previous research has been conducted in preclinical models. Extrapolation to the clinic will need to be tested stringently in well-designed clinical trials based on consideration of NK1R isoform expression (full-length vs truncated), tumor type, hormone receptor status, and treatment history. Biomarker-based selection of patients and prediction of response to therapy against NK1R will be indispensable for the effective deployment of NK1R-targeted therapies.
Lastly, the SP/NK1R axis is a new multi-potential therapeutic pathway for BC with potential to increase the efficacy of treatment, decrease toxicity, and overcome drug resistance. Future study and clinical validation could render NK1R antagonists the new standard therapy regimens for BC, giving patients new hope, especially aggressive or resistant ones.

Medical AI: From Data to Diagnosis
This study discusses the role of artificial intelligence in medicine; however, no AI techniques were applied in the research process.

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Authors' Contribution
Morteza Yousefi Darani: Designed the study and supervised the project. Zahra Aalipour Hafshejani: Conceptualization and writing—original draft. Mohammad Aghebati: Table preparation and manuscript revision. Alireza Shirzadi: Data collection and manuscript revision. All authors reviewed and approved the final version.

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Conflict of Interest
None declared.

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Table 1. Preclinical studies targeting the neurokinin-1 receptor system in cancers, including BC

Experiment	Type of cancer	Year	Antagonist	Effect on BC	Target	Ref.
MDA-MB231	BC	2005	MEN 11,467 (NK-1) and nepadutant (MEN 11,420; NK-2)	decreasing tumor cell proliferation	NK1R	(58)
Tumorigenic cells produced Substance P (ZR75–30, BT-474, T47D, DU4475, MDA-MB-330, and BT483)/ Nontumorigenic cells indicated undetectable substance P (MCF12A, MCF12F, Hs578Bst, MCF10A, and MCF10-2A)	BC	2005	C-99,994	decreasing tumor cell proliferation with no apoptosis	NK1R-Tr	(64)
human BC cell line (T47D)	BC	2010	SR140333	decreasing tumor cell proliferation / inducing apoptosis	NK1R	(63)
Human BC (MDA-MB-231, T47D, MCF-7, and SK-BR-3 cell lines)/ nontumorigenic mammary epithelial cell line (HBL-100)	BC	2013	ASN-1377642 (a non-peptide)	decreasing the phosphorylation of the ERK1/2 signaling pathway / diminishing proliferation in tumor cells with high expression of NK1R-FL in short-term therapy and hindering proliferation in tumor cells with high Nk1R-Tr expression in long-term therapy conditions	NK1R-Tr and NK1R-Fl	(26)

human BC cell lines (MT-3 / MCF-7 / MDA-MB-468 / BT-474)	BC	2014	L-732,138 L-733,060 Aprepitant	Inducing cell apoptosis in tumor cells / decreasing tumor cells' proliferation and migration / inhibiting tumor cell growth / shrinking tumor size / decreasing angiogenesis	NK1R/SP	(57)
metastatic (4THM, 4TBM, 4TLM, 4T1) and non-metastatic (67NR) BC cells	BC	2018	RP 67580 and GR 159897	Inducing cell apoptosis in tumor cells / decreasing tumor cells proliferation / the level of NK1R-Fl expression in 67NR is lower than in 4T1 / the effect of this antagonist is more significant in 4TLM and 4T1 than 4TBM and 4THM, such that the proliferation in the first two mentioned cell lines is completely inhibited compared to the second two mentioned cell lines/ hindering the function of SP	NK1R / NK2R/ SP	(62)
BC cell lines (MCF-7 / MDA-MB-468)	BC	2022	17-trifluoromethyl phenyl Trainor prostaglandin F2α (PGF2α)	decreasing tumor cell growth / hindering the mitogenesis-induced SP / decreasing the tumor cell proliferation / diminishing the quantity of cells in the G0/G1 and S cell cycle stages / provoking the Bad and Bax expression, leading to apoptosis in cancer cells	NK1R	(70)

Ref: Reference; BC: Breast cancer ; MDA-MB-231, ZR75-30, BT-474, T47D, MCF-7, DU4475, MDA-MB-330, SK-BR-3, MT-3, MDA-MB-468 , and BT483: Human breast cancer cell line; MCF12A, MCF12F, Hs578Bst, MCF10A, MCF10-2A, and HBL-100: Non-tumorigenic human mammary epithelial cell line; 4THM / 4TBM / 4TLM / 4T1: Metastatic mouse breast cancer cell lines ; 67NR: Non-metastatic mouse breast cancer cell line; NK1R: Neurokinin-1 receptor; NK2R: Neurokinin-2 receptor ; NK1R-FL: Full-length NK1 receptor isoform; NK1R-Tr: Truncated NK1 receptor isoform; SP: Substance P; G0/G1 phase: Cell cycle quiescent/growth phase; S phase: DNA synthesis phase; ERK1/2: Extracellular signal-regulated kinases 1 and 2; Bad / Bax: Pro-apoptotic proteins involved in mitochondrial apoptosis

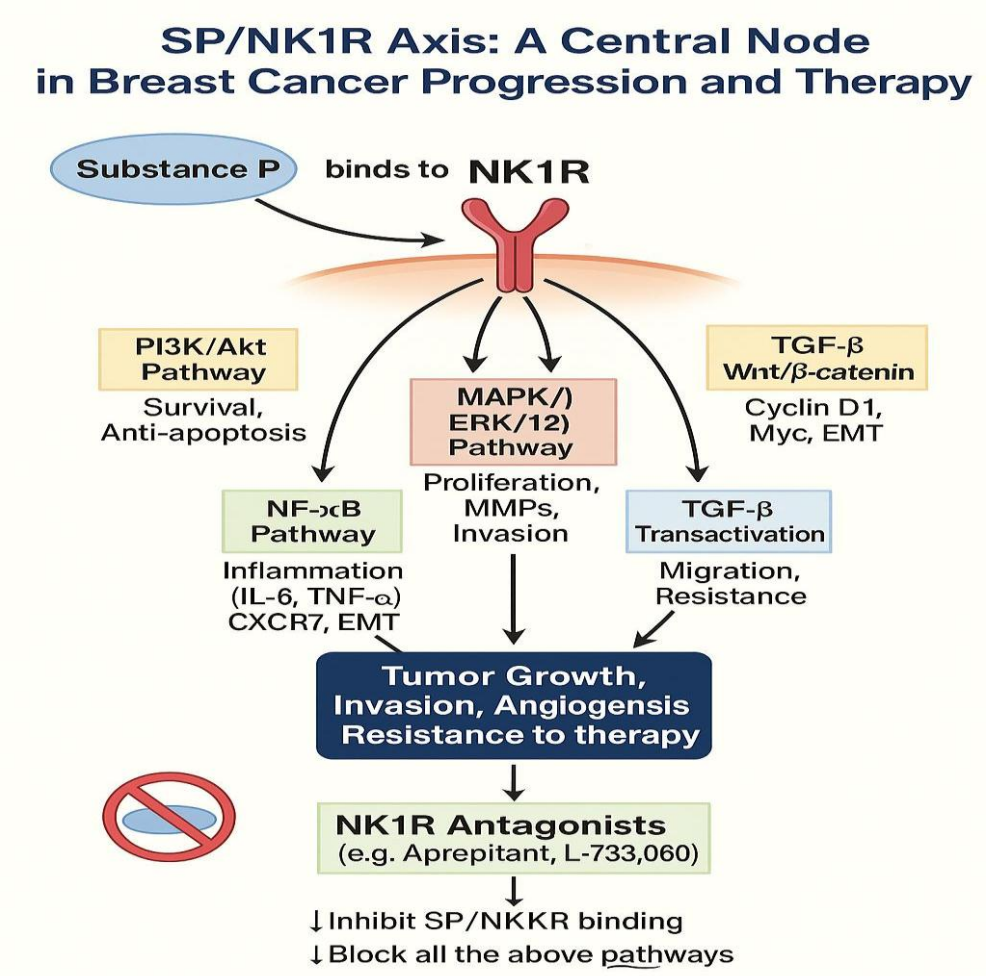

Figure 1. Schematic representation of the SP/NK1R axis as a mediator of BC progression. SP, a neuropeptide, signals through the NK1R that is present on BC cells and phosphorylates numerous oncogenic pathways. These involve PI3K/Akt activation (survival and anti-apoptosis), MAPK/ERK1/2 (proliferation and migration), NF-κB (generation of inflammatory cytokines like TNF-α and IL-6), and transactivation of EGFR and HER2 (resistance and angiogenesis). SP/NK1R also has cross-talk with TGF-β and Wnt/β-catenin signaling that promotes epithelial–mesenchymal transition and oncogene transcription like cyclin D1 and c-Myc. They all play a role in tumor growth, invasion, and resistance to drugs. NK1R antagonists like aprepitant, L-733,060 block SP binding and interfere with downstream signal transduction pathways, which lead to reduced tumor growth and enhanced therapy response with the added advantage of inhibiting chemotherapy-induced inflammation.

SP: Substance P; NK1R: Neurokinin-1 receptor; PI3K: Phosphoinositide 3-kinase; Akt: Protein kinase B; MAPK: Mitogen-activated protein kinase; ERK1/2: Extracellular signal-regulated kinase 1/2; NF-κB: Nuclear factor kappa B; TGF-β: Transforming growth factor beta; MMPs: Matrix metalloproteinases; EMT: Epithelial–mesenchymal transition; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor alpha; CXCR7: C-X-C chemokine receptor type 7; Myc: Myc proto-oncogene