

A comprehensive review on neurokinin-1 receptor antagonism in breast cancer

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ABSTRACT

Breast cancer is one of the most prevalent cancer types globally, and has caused more deaths in women. The undecapeptide substance P is participated in various physiological processes like emesis, pain, inflammation, antitumor activity, and also regulates the function of gastro intestinal tract and central nervous system by binding to NK1R. substance P (SP)/NK1R regulates the proliferation, migration, and metastasis of breast cancer cells and also controls the proliferation of endothelial cells for angiogenesis. It exerts an antiapoptotic influence as well. In breast cancer, NK1R is over expressed. It has been demonstrated that the NK1R antagonist inhibits the breast cancer cell proliferation in a concentration dependent manner, induces the cell death by apoptosis and inhibit angiogenesis. The antagonists of the NK1 receptor are safe and well tolerated. In this paper, we reviewed the extensive studies that have been done on the SP/NK1R system in breast cancer. In fact, only currently available are NK1R antagonist Aprepitant and its analogues. The research must, therefore, focus on drugs with elevated anti-tumor activity with lesser side effects. Modulating the function of the NK1 receptor as a therapeutic strategy is, therefore, the most attractive area of research for the design and creation of new molecules with important clinical values for the future.

INTRODUCTION

Cancer has been one of the most threatening human diseases for years. Approximately in 2020, 1,806,590 new cancer cases and 606,520 cancer deaths have been diagnosed in US (Siegel *et al.*, 2020). 18.1 million cancer cases have been reported worldwide in 2018 and 9.6 million cancer cases would lead to expected deaths. As per the GLOBOCAN project of the International Cancer Agency in India, cancer growth is expected to double in the next 20 years, from more than a million new cases in 2012 to greater than 1.7 million cases by 2035 (Mallath *et al.*, 2014).

Presently, breast cancer (BC) is the most predominant form of cancer among females, and several cancer studies have been reported (Toğaçar *et al.*, 2020). In 2019, 268,600 new invasive breast cancers among women and 2,670 cases in men

were diagnosed in the study (Miller *et al.*, 2019). There are many types of cancer documented. Breast cancer therapy requires either substance or drug inhibiting the cancer growth by interacting with the functioning of some molecules responsible for cancer growth and cell survival (Mittendorf *et al.*, 2016; Rugo, 2016).

Breast cancer cells may over express certain receptors, which triggers signalling pathways and further it regulates gene transcription for tumour proliferation, invasion, migration, and angiogenesis (Pal *et al.*, 2011). It controls gene transcription pathways for tumour proliferation, invasion, migration, angiogenesis, and more (Pal *et al.*, 2011). There are different kinds of pathways or receptors that are active in breast cancer. In this way, the P/NK1 receptor system also plays a pivot role in the pathogenesis of breast tumour (Masoud and Pagès, 2017).

NK1 receptor activation acts as a mitogen which is involved in mitogenesis, angiogenesis, cell migration, and metastasis (Mehboob *et al.*, 2015). NK1R inhibition suppresses cancer growth in many forms of cancer, creating an interesting target for cancer (Palma *et al.*, 2006). Human tumour cells have NK1 receptors that are over-expressed than normal human cells (Munoz *et al.*, 2010; 2011).

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Substance P is an 11 amino acid neuropeptide consisting of a particular C-terminal sequence of phe-x-gly-leu-met-NH₂, encoded by the gene tachykinin 1. Substance P is amphiphilic in nature, where the N-terminal has a positive charge and the C-terminal has a negative charge (Lazarczyk *et al.*, 2007; Muñoz and Coveñas, 2014).

Substance P has a good affinity with the NK1 receptor, a G protein coupled receptor (GPCR) and encoded by the TACR1 gene (Garcia-Recio *et al.*, 2013). It has two isoforms with 407 residues, a maximum length and a low-affinity NK1R-T receptor with 311 amino acids, a truncated one, such as the high-affinity NK1R-F receptor. The NK1 receptor has three extracellular (EL1, EL2, and EL3) transmembrane domains and three intracellular coils (C1, C2, and C3). The C-terminal is extended into a cell's cytoplasm. The intracellular region is related to heterotrimeric G protein-coupled with α , β , γ subunits, and guanosine diphosphate (GDP) (Garcia-Recio and Gascón, 2015; Lazarczyk *et al.*, 2007).

Substance P/NK1R system is involved in several physiological and pathological processes such as paracrine and endocrine secretions, dissemination of pain, vasodilation, and development of cells. Anxiety, stress, emesis, and depression are also associated with it. In multiple cancer cell lines, such as breast carcinoma, malignant gliomas, metastatic melanomas, ovarian and prostate cancer, various *in vitro* studies have shown that SP and NK1 receptors are increased (Garcia-Recio and Gascón, 2015; Mayordomo *et al.*, 2012; Rosso *et al.*, 2012).

Although, earlier research on function of substance P/NK1 receptors in breast cancer provided finite data on the recruitment of substance P/NK1R in the potential therapeutic regimen as a target. The scientific papers on the association substance P/NK1R system in the progression of breast cancer were summarized in this study.

Evidences association with substance P/NK1R and breast cancer

No intensive study on the P/NK1R mechanism in breast cancer pathogenesis has been performed. Some recent studies, however, have reported:

- I. The study conducted by Mehboob *et al.* (2020) stated that immunohistochemistry showed the expression of substance P/NK1R, where 68% of breast cancer cases reported overexpression of SP. 82.6% of SP-positive cases were associated with <60 years of age, 52.17% of SP-positive cases were seen in premenopausal women, and 47.82% in postmenopausal women. In addition, 82.6% of the interaction between SP and estrogen receptor (ER) and 78.2% between SP and human epidermal growth factor receptor (HER) were recorded in the research. Overall, the studies suggest that patients with breast cancer express SP/NK1R and also display the relationship between SP, ER, and HER.
- II. In another study by Dvoodian *et al.* (2019), 41 females with breast cancer and 34 healthy individuals were studied. Serum levels of Breast cancer patients (16.11 + 3.320 ng/ml) showed substantially high levels of SP than healthy persons (5.05 + 1.087 ng/ml). Moreover, based on the severity of staining, the percentage of NK1R was calculated where, 80% tumor biopsies among samples recorded higher percentage of stained cells than control (20%). In addition, 90% of the tissue distribution was seen in tumor biopsies and 10% of the tissue distribution was seen in healthy groups. Furthermore, real time polymerase chain reaction (RT-PCR) study showed a rise of NK1R mRNA in BC. Overexpression of NK1R is seen as usual in the membrane, cytoplasm, and BC nucleus. Finally, the analysis examined SP levels and the important association between SP/NK1R, tumor size, and HER-2 in breast cancer patients than normal individuals.
- III. SP induced cell migration in a dose-dependent manner compared to the control group, according to the Silvia Gutierrez report. The study further supported the association between nociceptive afferent neurons and tumor cells that also spread disease and pain. This effect was demonstrated by the release of kininogen by SP with pronociceptive and protumorigenic function. SP also enhances the expression of cognate receptors like NKR2, RAMP1 and CALCRL (Gutierrez and Boada, 2018).
- IV. The Nizam and Erin (2018) research tested both NK1 and NK2 receptors in Balbe mice breast carcinoma cells. In non-metastatic 67N cells, full-length NK1R showed lower expression than in metastatic cells. By inhibiting the activity of NK1R, they also investigated the anti-proliferative effects of RP67580 (NK1R antagonist). Admittedly, RP67580 at 30 μ m conc inhibits cell proliferation in 4TBM and 4THM at 76 5.477% and 76 4.55%, respectively. In addition, RP67580 decreases MIP-2 at the same concentration and also induces phosphorylation of the protein kinase B (AKT) without altering the extracellular-signal-regulated kinase (ERK). MIP-2, an angiogenic and inflammatory chemokine which causes cancer cell metastasis, is highly secreted by breast cancer cells.
- V. The findings of the Garcia-Racio *et al.* (2015), study showed that the proinflammatory cytokine / substance P co-activation of HER-2 and epidermal growth factor receptor (EGFR) in BC is a c-Src and matrix metalloproteinases (MMP) based mechanism. They documented the SP induced phosphorylation c-Src Tyr41 with the aid of time course studies. In addition, NK1 antagonists have been documented in Sk-BR-3 and BT 474 cells to significantly block c-Src phosphorylation. In addition, in the Sk-BR-3 and BT 474 cell lines, the NK1 antagonist substantially inhibit the phosphorylation of c-Src. Non-significant inhibition was observed in the MDA-MB-453 and MDA-MB-468 cell lines. In addition, the triple inhibition of NK1R leads to down regulation of c-Src phosphorylation and is probably caused by tachykinin signaling in BC cells.
- VI. The study by Munoz *et al.* (2014), documented the expression of mRNA for NK1R in MCF-7, MDA-MB-468, MT-3, MCF-10A, and 12A human cells with the assistance of Western blot analysis and PCR analysis. The NK1R expression was further shown by RT-PCR analysis using the β -actin as a control. The ratio was 1.6 + 3.9 for the non-tumor cell line HEK-293 and 1.8 + 1.92 for MCF-12A and 2.1 + 1.96 for the cell lines of epithelial breast cancer MCF-10A. Therefore, in BC cells and normal cell lines, 20%–60% of NK1R mRNA levels were higher. In addition, the study performed on aprepitant, L-733,060, and L-732,138 antitumor activity and demonstrated maximum NK1R activity inhibition in

dose dependence manner. NK1R and SP immunoreactivity in BC cells and apoptosis were also observed by the staining technique of DAPI.

DISCUSSION

In this study, the complements and results of previously published research findings on the role of the SP/NK1R system in BC cell metastasis were reported. The NK1 R expressed on the cytoplasm and plasma membrane in BC cells by immune receptor activity was documented in one of the studies (Esteban *et al.*, 2009; Muñoz *et al.*, 2010). The activated SP/NK1 R system activates the signaling cascade causing mitogen activated protein kinases (MAPKs) to lead to cell calcium mobilization and phosphoinositide hydrolysis (Kim *et al.*, 2019) and the Akt pathway phosphorylates shown in the figure (Backman and Danielson, 2013). Furthermore, the activation of PI3K-, NF-kB pathways increase after binding of SP with NK1R (Fig. 1) (Mayordomo *et al.*, 2012; Reddy *et al.*, 2009).

In regards to nociception BC cells secretes SP. Increased level of SP modulates inflammatory cytokinin’s like IL4, IL6, and IL10 by increasing the permeability of blood brain barrier(BBB) (Kim *et al.*, 2019; Mehboob *et al.*, 2020; Rodriguez *et al.*, 2014). In addition, it contributes to cell division, cell progression, vasculogenesis, and metastasis by step-down apoptosis via antiapoptotic protein kinase (Muñoz *et al.*, 2014). Earlier studies suggested that the SP induced BC cell adhesion and transmigration over the human brain microvascular endothelial cells (HBMECs) where, it is independent of the mediated pathway of MMP-9. SP induces proinflammatory cytokine activation and loss of quiescence and causes HBMECs to become destabilized via Tumor necrosis factor- α and Ang-2 secretions. Both of these molecules strengthen angiogenesis and migration of inflammation cells (Rodriguez *et al.*, 2014; Scharpfenecker *et al.*, 2005).

Activated GPCR is slightly regulated in certain cancer cell types by transmodulation of the endothelial growth factor receptor, like tyrosine kinase activity receptor EGFR, HER2,

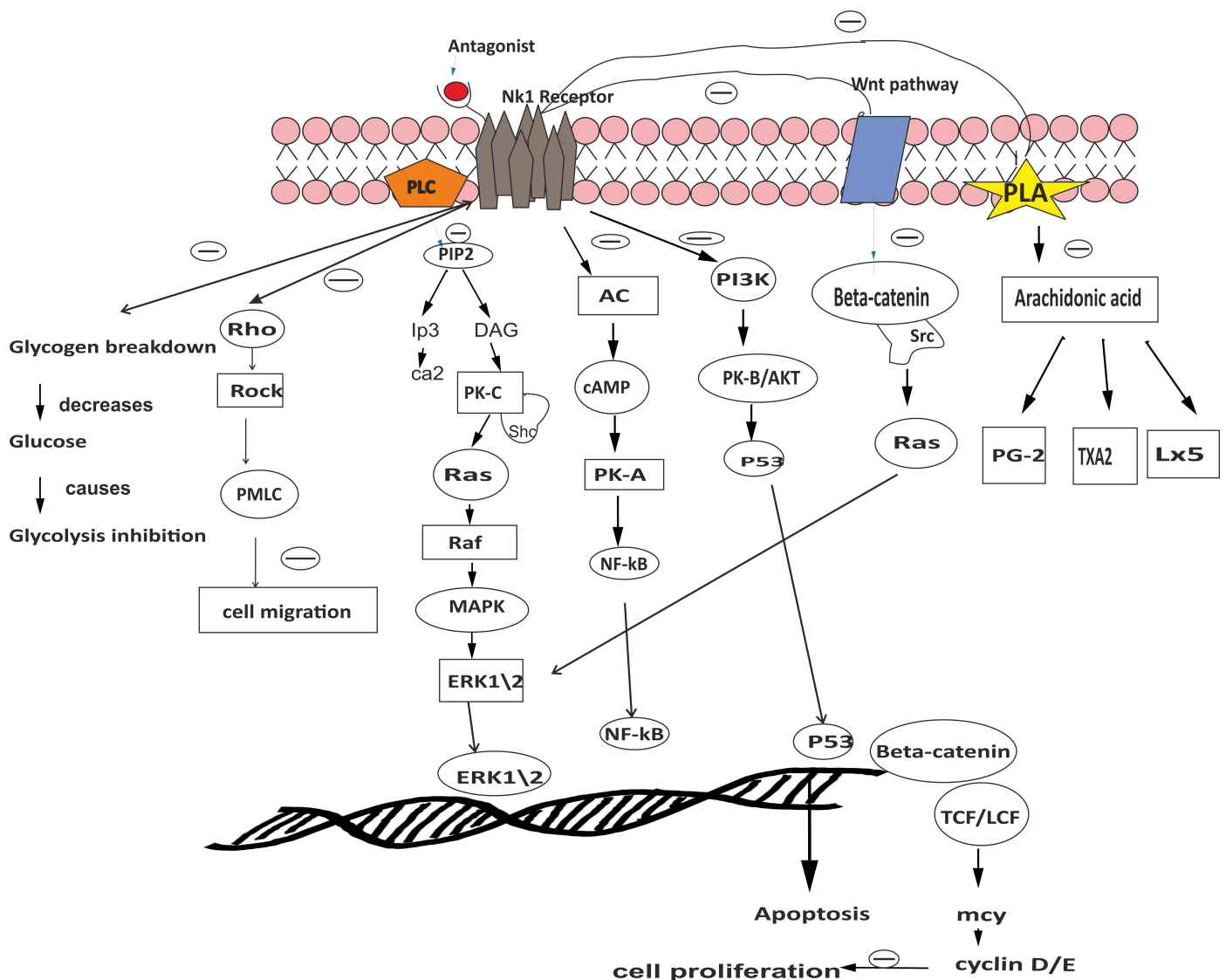


Figure 1. Explains a brief mechanism of NK1 R antagonist (Aprepitant) in breast cancer.

HER3, and HER4 (Olayioye *et al.*, 2000; Stern, 2000). These pathways indicate a crucial role in initiating the development of the tumor. HER-2 is especially over-expressed in BC, approx. 25% and linked to poor prognosis and high mortality rate. Garcia *et al.* (2013), stated the SP induced proinflammatory cells enhance cancer cell progression by activating the EGFR, HER2. In addition, an *in vitro* study stated that increased SP exposure enhances the expression of EGFR and HER2 in cell lines. NK1R antagonism is also synergistic with anti-EGFR and anti-HER2 therapies and has demonstrated a substantial decrease in cell survival. Dual inhibition of these receptors may be the new strategy in cancer treatment.

The persistent activation of HER2 by SP autocrine signaling, which develops tumor pathogenesis and drug resistance in BC, was determined in one study (Garcia-Recio *et al.*, 2013). Patients may feel pain during cancer metastasis and this is due to excessive sensory nociception activation associated with peripheral sensors. This leads to excessive release of neuroinflammatory peptides like Substance P, calcitonin gene-related peptide, and neurokinin A.

The SP raises MDA-MB-231LUC chemokines and further improves the acute release of Kininogen, Silvia Gutierrez, and Danilo said. In total, it demonstrates pronociceptive and pro-tumorigenic roles and promotes metastasis of the bone marrow. This demonstrates the link between the sensory nociception neurons and the progression of cancer (Gutierrez and Boada, 2018; Huang and Korlipara, 2010).

The main function of SP/NK1R system in the cancer development has thus been suggested on the basis of recent scientific evidence (Munoz *et al.*, 2011). It is extensively located in central and peripheral nervous system and displays a great affinity toward NK1R. It was clarified that inhibition and BC recurrence could be significantly involved in SP and NK1R (Muñoz *et al.*, 2010) and moreover in tumor cell viability. The activation SP/NK1R system induces mitogenesis and cancer proliferation, growth of blood capillaries, and neoangiogenesis (Bigioni *et al.*, 2005; Huang *et al.*, 2010; Mayordomo *et al.*, 2012; Muñoz *et al.*, 2014). NK1R antagonists inhibit both DNA synthesis and cell proliferation via the MAPK pathway.

Aprepitant (NK1R antagonist) is approved by the Food and Drug Administration and is widely used to treat nausea and vomiting caused by chemotherapy. Cell apoptosis is increased and the pathways of Akt/p53 are blocked (Bayati *et al.*, 2016; Li *et al.*, 2016; Mayordomo *et al.*, 2012; Munoz *et al.*, 2011; Quartara *et al.*, 2009). NK1R antagonists such as aprepitant and L-732,138 completely attenuate the BC cell growth and induce apoptosis further. In addition, other forms of cancer such as pancreatic cancer, laryngeal cancer, retinoblastoma, neuroblastoma, glioma, melanoma, retinoblastoma, colon and gastric cancer have demonstrated anticancer activity (González Moles *et al.*, 2008; Muñoz and Rosso, 2010; Muñoz *et al.*, 2007, 2008, 2010).

In addition, the NK1R antagonist also prevents the development of the β -arrestin complex that allows ERK1/2 translocation into the cell nucleus; attenuates cell proliferation and induces the mortality rate of cancer cells. The NK1R antagonist reduces phosphorylation of Akt, leading to poly polymerase (ADP-ribose) polymerase proteolysis and caspase-3 cleavage (Akazawa *et al.*, 2009; DeFea *et al.*, 2000). Munoz confirmed

that, for 45 days, a patient suffering from chronic obstructive pulmonary disease and non-small cell lung carcinoma underwent radiotherapy along with Aprepitant. Patient showed positive signs without adverse effects and even with decreased tumor volume (Muñoz *et al.*, 2019; Shaik-Dasthagirisaheb *et al.*, 2013).

CONCLUSION

Recent findings strongly supporting the role of the SP/NK1R system in the pathogenesis of breast cancer and associated with poor prognosis were examined. The evidence indicates that NK1R antagonists provide a great opportunity for researchers to further synthesize and modulate NK1R-active compounds as a potential cancer management therapeutic agent. In addition, in order to provide full evidence of NK1R antagonist effects in breast cancer treatment, more clinical studies must be undertaken.

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