Review paper

# The role of substance P in cancer promotion and progression

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## Abstract

Cancer is a chronic global problem, and is the leading cause of mortality in Australia. Metastasis is a key characteristic of malignant tumors, enabling the cancer cells to move from their primary site to a secondary location. This process of translocation of cancer cells and transmigration through the blood vessels is similar to what is seen with immune cells during the inflammatory process. Substance P (SP) is known to be a significant mediator in the development and progression of inflammation, and it has been suggested that it may play a similar role in relation to metastatic tumor development via tachykinin NK1 and NK2 receptors. Therefore, the development of antagonist molecules for the NK1 receptor presents an important opportunity for exploiting these molecules as novel therapeutic agents for the treatment of cancer.

**Key words:** cancer, metastasis, inflammation, substance P.

## Objective

The aim of this literature review is to examine the potential role that substance P (SP) may play in the promotion and progression of cancer and in particular in metastasis. This literature review involved searching online databases and electronic resources, including PubMed, PubMed Central (PMC), Medline, Health Reference Center Academic, and Academic Search Premier. The key words used to research the subject were: cancer, metastasis, inflammation, and SP. No date limits were applied to the articles included in the review.

## Background

Cancer is a major problem worldwide, and is the leading cause of mortality in Australia. Particularly in countries with aging populations, there is a potential for further increases in its incidence worldwide. Cancer is not only a leading cause of mortality, but it also has negative effects on quality of life, family relationships, functional status, and social functioning. In addition, it has a range of economic impacts, including health care costs, employability, productivity, and insurability [1].

The term neoplasm or (tumor) refers to a new growth or abnormal mass of tissue which does not obey the growth laws of a normal cell [2]. As such, they are characterized by progressive or uncontrolled proliferation of cells [3, 4]. Neoplasms may be classified as being benign

or malignant. Benign neoplasms grow slowly, are enclosed in a fibrous capsule, are limited to specific locations, and are considered as non-cancerous. Importantly, they do not cause death unless their location interferes with or affects vital body function [5, 6].

In contrast, malignant neoplasms have lost the ability to control both cell proliferation and differentiation. They are often fatal because the cancer cells can spread to distant sites through the bloodstream, lymphatic system, or through body spaces [5–9]. Cancer metastasis is the major reason for the failure of treatment, as well as the leading cause of mortality in individuals with malignant tumors [7, 10, 11]. Thus, understanding the process by which tumor cells develop heterogeneity, invade local tissues, and spread to distant tissues is a major goal of cancer research. An improved understanding of the metastatic process may enable the development of more effective therapies for a variety of different cancers.

## Metastasis

Invasion and metastasis are key characteristics of malignant tumors, enabling the cancer cells to move from their primary site to a secondary location. Metastasis is the movement of tumor cells to sites which are distant from the primary tumor. The adaptation to create a favorable site for tumor growth involves the interaction between tumor cells and the host microenvironment and is governed by the same factors that directed proliferation at the primary site [12, 13]. Also, the implantation of tumors at secondary sites is not merely a random process but rather a "seed and soil" guided event [13].

The spread of cancer cells may happen by penetration of bloodstream, lymphatic tissue or via spaces surrounding organs [10, 11, 14]. As with benign neoplasms, malignant tumors arise as a result of cancer cells lacking the ability to balance cell division and cell death (apoptosis) [7, 9]. However, in addition to this, they possess a variety of other characteristics that contribute to their metastatic potential. One of the critical first steps is that they can form their own vascular supply through the process of angiogenesis [10, 11]. Furthermore, "these transformed cells lose the ability to communicate and interact with each other which enables them to penetrate neighboring tissues and finally spread via the bloodstream, or lymphatic system to distant sites" [1, 10, 11]. Invasion usually happens before metastasis, which means the tumor cells infiltrate the surrounding tissues [6, 14]. Most cancer cells secrete proteases (MMP1, MMP2), which enable them to break down the extracellular matrix of the surrounding tissue and thus facilitate the invasion process [5, 15–17].

### Mechanisms associated with metastasis

Metastasis happens through many stages [14, 18, 19]. These are listed as follows (Figure 1):

- Detachment of cancer cells from each other and from primary tumor.
- Attaching to matrix components which consist of collagens, proteoglycans and glycoproteins and then degradation of the extracellular matrix.
- Migration of cancer cells, by invasion of blood vessels or lymphatic vessels and scattering and seeding these cells to distant sites.
- Occupying and settling of cancer cells in blood vessels of distant organs.
- Penetration of cancer cells via the vessel walls and into the tissue of secondary locations.
- Finally enlargement and growth of tumors at secondary locations.

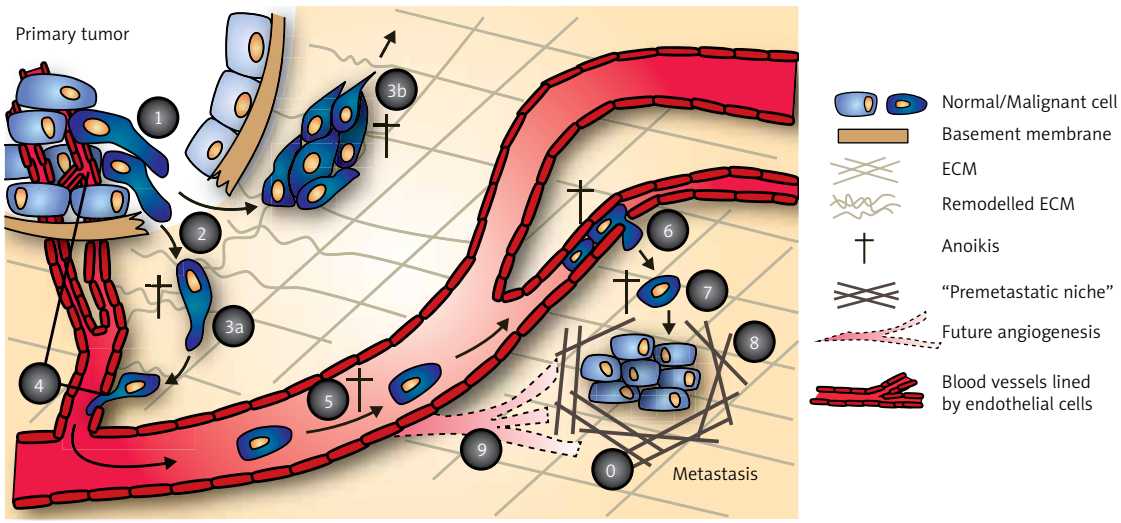


**Figure 1.** Metastasis

There are many factors that facilitate the spread and migration of cancer cells from the primary tumor to distant areas. One of the initial steps is that cells in the primary tumors lose their adhesion molecules which bind them to neighboring cells, and this can contribute to the spread of cancer [16, 20]. Other key factors are the release of chemical mediators, the ability to survive in a hypoxic environment, and the ability to escape detection by the immune system [16, 20, 21].

Moreover, tumor development and progression are multifactorial processes, regulated by a large variety of intrinsic and micro-environmental factors [11]. A key role in cancer is played by members of the chemokine superfamily. Chemokines, growth factors with their receptors, are expressed by tumor cells and by host cells which stimulate proliferation, and angiogenesis and metastases [4, 14]. In addition, it has already been suggested that secretion of proteases by cancer cells plays a role in the loss of cancer adhesiveness and helps release these cells from the primary tumor mass [4, 14]. Thus, the specific organ microenvironment determines the extent of cancer cell proliferation, angiogenesis, invasion, and survival. Therapy of metastasis should therefore be targeted not only against tumor cells, but also against the host factors that contribute to and support the progressive growth and survival of metastatic cancer cells [4, 22].

Furthermore, migration of cancer cells throughout the body is not enough to cause distant tumors, because the cells should not be capable of surviving within environmental conditions which are completely different from those of their tissue of origin. For example, blood and lymph, which are the main pathways for the spread of cancer cells, are hostile environments for cells not adapted to surviving in that environment [23, 24]. It is estimated that only about 1% percent of cancer cells that enter the circulation survive to form secondary tumors [25, 26]. When the cancer cell introduce the circulation, it will face several challenges which reduce the chances of its survival including the fast flowing blood, immune response attacks by antibodies of the white blood cells, and apoptosis signals induced by loss of cell contact as well as rocking of cells against the wall of blood vessels [23, 25, 26]. In addition, blood serum contains waste products, and other substances that are toxic to cancer cells including excess water, carbon dioxide ($CO_2$), salt (such as those of sodium and potassium), plasma proteins (such as albumin, globulins, and fibrinogen), and metabolic wastes (such as urea) circulate in the plasma [4, 5, 13, 27].

There are some locations where metastases occur more frequently; for example, the liver, lungs, lymph nodes, brain, bone marrow and adrenal glands are regarded as common sites of secondary tumors, while the heart and skeletal muscle are rarely affected. Thus, it is obvious that some of kind of selectivity has to exist in the development of secondary tumors [12] (Figure 2).

The process of transportation of cancer cells and transmigration through the blood vessels is similar to what happens during the inflammatory process [28, 29].

## Inflammation

It is the reaction of tissues to any injury, beginning with vascular dilatation, slowing of blood flow and increased vascular permeability [29]. A central function of inflammation is the movement of leukocytes (neutrophils, monocytes and eosinophils) from the vascular compartment to the site

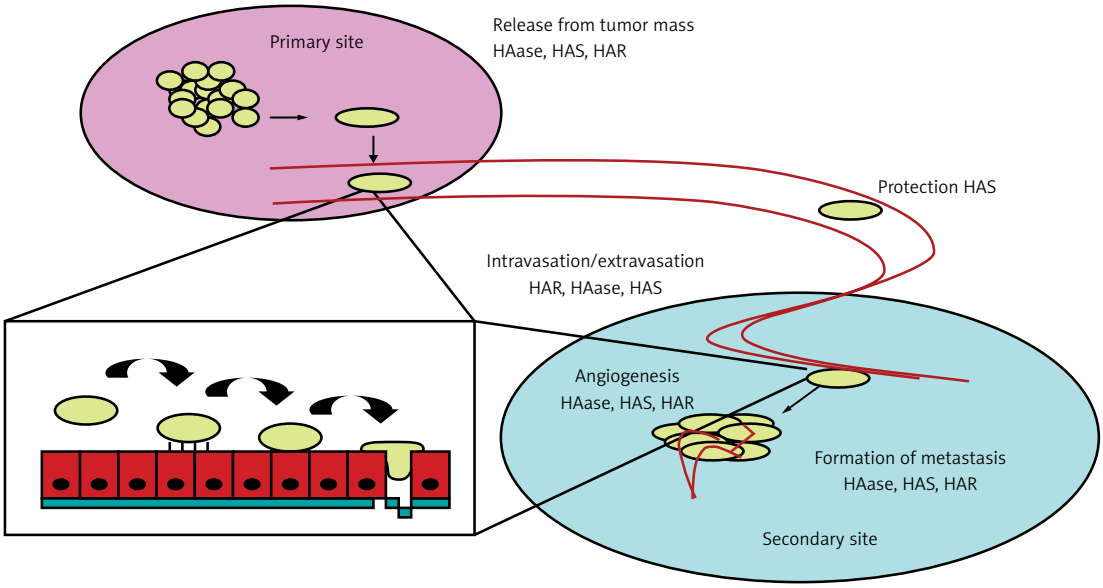


**Figure 2.** Clinical stages of metastasis

of injury to combat the offending stimulus, either ingesting them or releasing the appropriate antibody [29]. Extravasation is the sequence of events in the movement of leukocytes from the vascular lumen to the interstitial tissue which occurs in a stepwise manner [29, 30] as follows:

Firstly, individual and rows of leukocytes slowly stumble along the endothelium and adhere to the endothelium. This is called pavementing and is a receptor-mediated mechanism. After adhesion, leukocytes insert pseudopods into junctions between the endothelial cells and pass across the basement membrane to escape into the extravascular space in the extravasation stage, which is the physical point of cells to exit the blood vessels to the inflamed or irritated site. Leukocytes secrete proteases such as MMPs which are a group of proteolytic enzymes whose main function is to degrade extracellular matrix (ECM) protein [31], and "Up-regulated expression of MMP members is often associated with the presence of inflammation" [32]. Moreover, studies revealed that inflammatory cells can induce the expression of MMPs which are crucial for all stages of the inflammation from tissue repair, foreign body elimination to activating cytokines [33]. On the other hand, MMPs have been implicated in cancer progression and invasion and are highly expressed in a variety of cancers and studies, suggesting that MMPs induced by inflammatory cells promote angiogenesis, a significant requirement in tumor invasion [31, 34, 35].

Thus, there may be common mechanisms associated with inflammation and metastatic tumor development including chemical mediators that facilitate these processes [29, 36, 37].

## Inflammation and cancer

There is evidence supporting the concept that chronic inflammation and continuous irritation participate in cancer development and progression [28], and Hahn et al. identified inflammation as the seventh hall mark of cancer. Further, recent research indicated that inflammation highlights several aspects of tumor growth, survival and most significantly metastasis [38].

There are data indicating that many molecules and their activities are implicated in the inflammatory microenvironment and tumor progression [36, 37]. This might be due to the inflammatory cells and immune-modulatory mediators such as histamine, serotonin, bradykinin and SP which likely can impact on cancer promotion by secreting cytokines, chemokines, protease and growth factors which induce proliferation and invasiveness of cancer cells [39–42].

Furthermore, both interleukin-31 (IL-31) and interleukin-33 (IL-33) that are derived from mast cell proteases are implicated in cancer pathogenesis, and there is evidence supporting the concept that the presence of inflammatory cells and immune-modulatory mediators IL-31 and IL-33 in the tumor microenvironment are implicated in tumor progression and metastasis such as elevated expression of IL-33 in tumor tissues of colorectal cancer (CRC) patients [43]. In addition, population-based studies demonstrated that 25% of all cancers are due to inflammation and almost every cancer type is infiltrated or surrounded by inflammatory cells [44].

Thus, not only may the use of anti-inflammatory drugs be helpful in the prevention of occurrence of several types of cancer but also they highlight the key role of inflammation in cancer like steroid and aspirin [45–47].

In terms of potential for inflammatory mediators that playing a role in cancer promotion and progression, there has been pro-inflammatory peptide, SP.

## Substance P

Substance P is a neuropeptide: an undecapeptide that functions as a neurotransmitter and as a neuromodulator. Substance P and its closely related neuropeptide neurokinin A (NKA) are produced from a polyprotein precursor after differential splicing of the preprotachykinin A gene [48].

In addition, SP is a member of the tachykinin family of neuropeptides and acts through interaction with the NK1 receptor (NK1R) [49]. Tachykinins have well-established roles in the innate and adaptive immune system [49]. NK1R exists in 2 isoforms, which are generated through alternative splicing: a full length NK1R that consists of 407 amino acids and is the predominant isoform in neuronal tissues, and a truncated NK1R that lacks the last 96 amino acid residues at the C terminus intracellular domain and is predominantly expressed in various non-neuronal cells, including monocytes, lymphocytes, eosinophil and macrophages [48, 50].

Substance P is released from the terminals of specific sensory nerves. It is found in the brain and spinal cord, and is associated with inflammatory processes and pain [48, 51]. In the spinal cord, SP is thought to be involved in carrying pain signals from the periphery to the CNS; thus, SP antagonists may be promising analgesics [52]. Another possible application for a SP antagonist in the CNS is the treatment of psychosis, based on the observation that SP modulates dopamine turn-over [53].

Furthermore, SP is not only widely distributed in both the central and peripheral nervous systems, but it is also ubiquitous in the human body [54]. Following SP release, SP binds to the tachykinin NK1 receptors. Release of SP is linked to a vari-

ety regulates of biological functions in the central nervous system, including emotional behavior, pain perception, stress, depression, anxiety, emesis, migraine, and alcohol addiction, in addition to its mediation of several pathophysiological processes [55].

In the peripheral nervous system and other tissues, it acts as a local hormone (tachykinin). It causes hypotension and vasodilatation and may cause contraction of smooth muscles [56, 57].

In addition, it is thought to be involved in the regulation of respiratory mechanisms, regulation of the cardiovascular system, sensory perception, in neuronal survival and degeneration, sensory perception, movement control, gastric motility, salivation and micturition [58, 59]. While these actions may be advantageous initially since SP is a potent vasodilator, long-term up-regulation of SP may have detrimental effects as long-term SP is associated with dilated cardiomyopathy (degeneration of heart muscle and heart enlargement), an important cause of heart failure among young adult [60].

Substance P is also involved in multiple processes including inflammation after binding to the tachykinin NK1 receptors [61].

## Inflammation and substance P

Over the past two decades, SP has been considered to be a significant mediator in the development and progression of inflammation [30, 61–63]. It acts as a vasoactive mediator, increasing vascular permeability and mediating the function of inflammatory cells. These impacts, collectively termed neurogenic inflammation, that comprise micro vascular plasma leakage, neutrophil recruitment, and inflammatory mediator synthesis [16, 30]. It has been thought that substance P is the most potent initiator of neurogenic inflammation due to its association with increased vascular permeability and subsequent plasma protein extravasation [64]. It also potentiates classical inflammation by stimulating the production of inflammatory mediators such as histamine, cytokines (such as IL-6) and kinins, in addition to interacting with adhesion molecules causing leukocyte migration [65].

In addition, it has been demonstrated that the effect of SP on the immune system is both pro- and anti-inflammatory and includes up-regulation of a number of cytokines and cell receptors because there is interplay between monocyte exposure to SP and recruitment into sites of inflammation [48].

It has been indicated that SP acts via NK1 and NK2 receptors to stimulating both intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM), which could play a major role in extravasation process, in addition to increasing the vascular permeability [30, 66–68].

Furthermore, there are data indicating that SP participates in inflammation by interacting with the NK1 receptor expressed on nerves (excitatory neurons and secretory cells) and inflammatory cells, such as macrophages, mast cells and T cells. The activation of these cells results in the release of cytokines and chemokines as active neuron factors and other neuropeptides that modify inflammation [30, 61, 67]. In addition there is increasing evidence that SP modulates the activities of a number of different leukocytes that characterize both the acute and the chronic inflammatory response [30, 66–68].

Also there are data indicating that SP is an important mediator in the development and progression of mucosal inflammation [58, 59]. This peptide, released from mucosal nerves, sensory neurons and inflammatory cells of the lamina propria during mucosal inflammation, participates in inflammation by interacting, directly or indirectly, with NK-1R expressed on nerves, epithelial cells, and immune and inflammatory cells, such as mast cells, macrophages and T-cells. SP-dependent activation of these cells leads to the release of cytokines and chemokines mediators and other neuropeptide that modulate inflammation [58, 59, 69].

There is a large body of evidence demonstrating that SP possesses a variety of potent effects, including the production of cytokines, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-1 (IL-1), IL-4 and IL-6 [70, 71]; SP selectively activates TNF-$\alpha$ synthesis in mast cells too [72]. Moreover, SP stimulates the release of TNF-$\alpha$, which mediates the expression of such adhesion molecules as E-selectin, ICAM-1 and VCAM-1 on vascular endothelial cells, thereby leading to leukocyte migration [73–75].

Additionally, SP may play a role in the pathogenesis of such diverse diseases as arthritis, asthma, and inflammatory bowel disease [76]. Also, multiple studies have documented the role of SP in viral, bacterial, and parasitic infection [77, 78].

In addition to its pro-inflammatory role, SP and its metabolites in combination with insulin-like growth factor-1 are shown to promote the corneal epithelial wound healing [79].

## Substance P and cancer

The first evidence that presence of SP/NK1 might contribute to cancer development and progression derives from the field of inflammation, because the role of chronic inflammation in carcinogenesis process was examined via many epidemiological studies of pro-inflammatory along with other factors that take part in the inflammatory response [36, 37, 80].

It has been demonstrated by many studies that SP acts via NK1R as a mitogen on several human

cancer cell lines such as (glioma, neuroblastoma, retinoblastoma, laryngeal carcinoma, and melanoma) by inducing growth factors and mitogen-activated protein kinases which are collectively called the mitogen-activated protein (MAP) kinase cascades which associated with cell proliferation and differentiation, or apoptosis of cells [81–83]. In addition, their presence in tumor microenvironment strongly suggests a role for the SP/NK1R complex in tumor development and progression [46, 47].

Therefore, the SP/NK1R system may play a role in the development of cancer, because SP may be a universal mitogen in NK1R expressing tumor cell type. In addition of their presence in microenvironment tumors strongly suggest a role for the SP/NK1R complex in tumor development and progression [46, 47].

Furthermore, NK1R, a receptor of SP, is overexpressed not only in several normal cells [46, 84], but also in neoplastic cell types [46, 85, 86]. It is also known that malignant tissues express more NK1 receptors than benign tissues. In addition, the tumor cells that express the most malignant phenotypes show increased NK1 receptor expression [87].

Furthermore, there are data indicating that substance P acting via the NK1 receptor probably plays some role in a number of biological functions related to cancer including angiogenesis, invasion and metastasis [47, 87–89]. The formation of new blood vessels from the endothelium of the existing vasculature (angiogenesis) is a significant process in tumor growth, progression, and metastasis [90, 91]. Inhibiting tumor angiogenesis seems to be a significant way to prevent tumor growth, progression, and metastasis, and it is a promising strategy for treatment of cancer. In addition, inhibiting the actions of substance P by blocking the NK1 receptor may be one approach to achieve this goal.

Moreover, substance P has been implicated as a mediator in cancer cell extravasation through the blood-brain barrier (BBB) to form cerebral metastasis [92]. Additionally, it has been reported that SP is involved in pancreatic cancer perineural invasion, and that SP induces cancer cell proliferation and invasion, as well as the expression of MMP-2 in pancreatic cancer cells [87].

It has been reported that activation of the neurokinin-1 receptor (NK1R) by substance P initiates several intracellular signaling pathways, including the nuclear factor-κB (NF-κB) pathway, culminating in the release of pro-inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF) [93, 94]. IL-1β and TNF, in turn, upregulate expression of the adhesion molecules involved in extravasation [95]; blocking the NK1 receptor has been shown to reduce expression of TNF [95]. Furthermore, the combination of SP and insulin-like growth factor-1 (IGF-1) significantly increased the number of cells attached to the fibronectin matrix, and increased the expression of integrin α5 [96].

Thus, the NK1 receptor might be a new promising target in the treatment of cancer, and offers a good opportunity for the development of antagonist molecules as novel curative agents [55, 97–99]. Hence, there is a need to explore research initiatives in cancer in this area and there is an interest in identifying the role of substance P in cancer promotion and progression, and a new path may be opened up to offer a future to cancer patients. Additionally, neurokinin-1 receptor antagonists might become a novel and promising approach and access for treating patients with cancer.

## Conclusions

Cancer is probably the most devastating and heterogeneous disease and is a major cause of mortality in Australia. The financial costs of cancer are high not only for the person with cancer but also for society as a whole, in addition to its negative impacts on the quality of life. Its potential for invasion and metastasis also increase its tendency to cause tissue destruction and capacity to cause death.

There is evidence supporting the hypothesis that inflammation provides conditions for the spread of cancer. Anti-inflammatory agents should be explored for both prevention and treatment of cancer. Their true potential will be recognized only through well-controlled clinical trials.

In addition to the significant role of substance P in inflammation, there may be a role for substance P in cancer promotion and progression after binding to NK1 receptors. Thus, the development of antagonist molecules of the NK1 receptor represents an important opportunity for exploiting these molecules as novel therapeutic agents.

## Conflict of interest

The authors declare no conflict of interest.

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