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## Paravertebral anesthesia: how substance P and the NK-1 receptor could be involved in regional block and breast cancer recurrence

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Aristotle's Techné Concept Knowledge and understanding belong to art (techné) rather than to experience, and we suppose artists to be wiser than men of experience; and this because the former know the cause, but the latter do not. For men of experience know that the thing is so, but do not know why, while the others know the 'why' and the cause.

(Metaphysics by Aristotle. Book I)

In a retrospective study, Exadaktylos et al. [1] reported a beneficial relationship between paravertebral block and cancer recurrence in women undergoing mastectomy and axillary clearance for breast cancer. In fact, these authors concluded that "breast cancer patients undergoing surgery with paravertebral anesthesia and analgesia combined with general anesthesia have a lower incidence of cancer recurrence or metastasis during the initial years of follow-up than patients undergoing surgery with general anesthesia and patient-controlled morphine analgesia" [1]. These authors speculated that regional anesthesia might attenuate

the perioperative factors that enhance tumor growth and spreading [1]. In this sense, regional anesthesia may help to maintain normal perioperative immune function by attenuating the surgical stress response by blocking noxious inputs mediated by substance P [2]. It is known that the stress response induces an inhibition of the immune function (i.e., there is a marked attenuation of natural killer cells, these cells being involved in preventing tumor dissemination) [3]. Paravertebral anesthesia also spares patients from postoperative opioids (e.g., morphine), which inhibit both cellular and humoral immune function [4, 5]; in addition, it is known that morphine exerts a proangiogenic effect [6]. In sum, the authors surmised that regional anesthesia and analgesia may help to preserve immune function by attenuating the surgical stress response and diminishing the need for opioids. However, until now the underlying mechanisms remain unknown.

The reason for this letter is to provide additional data that could support and explain the relationship between regional anesthesia, analgesia, and the recurrence of cancer. Many reports have clearly established an overexpression of neurokinin-1 (NK-1) receptors in tumor cells and others have reported the roles in which substance P (SP) is involved [7]. Summing up these investigations, it could be stated that:

1. SP, after binding to the NK-1 receptor, is involved in pain transmission and in neurogenic inflammation. Regarding pain transmission, both the neuropeptide and NK-1 receptors are located in the dorsal horn of the spinal cord. Noxious stimuli enhance SP release from C-fibers and then SP depolarizes dorsal horn neurons in a similar manner to when electrical stimulation of C-fibers is carried out. It is known that both responses are blocked by NK-1 receptor antagonists. SP is a pain

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neurotransmitter, and SP receptor antagonists, synonymous of NK-1 receptor antagonists, are analgesic. Moreover, the local administration of anesthetics, at concentrations such as those occurring after spinal or epidural anesthesia, inhibits the release of SP, this inhibition being non-competitive [8].

2. After binding to the NK-1 receptor, SP induces mitogenesis in tumor cells and exerts angiogenic activity, as well as inducing tumor cell migration. In fact, it has been reported that SP stimulates the migration of human breast carcinoma cells (MDA-MB-468), a prerequisite for invasion and metastasis [9, 10]. Moreover, SP exerts an antiapoptotic effect [7].
3. The presence of both SP [11] and NK-1 receptors in tumoral tissues, including breast carcinoma [10, 12, 13], has been demonstrated. This means that SP could act through an autocrine mechanism, through which SP is secreted from primary tumors. In addition, the peptide could also be released from peripheral nerve terminals.
4. Breast carcinoma cells express and release more SP and express more NK-1 receptors [13] than normal breast cells.
5. NK-1 receptor antagonists exert an antitumor action: (a) by inhibiting tumor cell proliferation in several tumor cell lines, including breast cancer cells [10, 13, 14]. NK-1 receptor antagonists induce cellular death by apoptosis [10, 14]; (b) by inhibiting tumor neoangiogenesis [15]; and (c) by inhibiting the migration of tumoral cells (e.g., breast carcinoma cells) [9, 16]. NK-1 receptor antagonists also block the mitogenic action exerted by SP on tumor cells.

The above data, among others, should lead us to reappraise about the role of the SP/NK-1 receptor system and anesthetics in tumor progression, angiogenesis, and in the incidence of invasion and metastasis. As mentioned, it has been reported that regional anesthesia and analgesia may help to attenuate the surgical stress response by inhibiting the release of SP from nerve fibers. Thus, according to the five key points indicated previously, the following question arises: Is such inhibition one of the causes for the increase in survival of patients receiving regional anesthesia before surgery for breast cancer in the report published by Exadaktylos et al. [1]? In this sense, SP could be one of the perioperative factors, suggested by Exadaktylos et al. [1], that increase tumor growth and spreading. Thus, by inhibiting the release of SP, this peptide could not induce the latter two actions. If this were indeed the cause, might the risk of recurrence be further reduced by administering the drug aprepitant (which binds to the NK-1 receptor and after binding to such receptor induces apoptosis in several human tumoral cell lines [17]) as an adjunct NK-1 receptor antagonist in the perioperative period? This

binding induces all the beneficial effects that NK-1 receptor antagonists exert on the tumor growth and spreading, which are reported in the key-point 5. These questions require future investigation for confirmation, but the background that we have commented leads us to believe that it is quite possible that, as in pain and in neurogenic inflammation, in tumor progression, in angiogenesis and in tumor cell migration (invasion and metastasis), the activation of the NK-1 receptors by SP plays an important role, and hence the SP/NK-1 receptor system, after being blocked with NK-1 receptor antagonists/regional anesthesia, could be involved in the recurrence of cancers overexpressing NK-1 receptors. Thus, the results reported by Exadaktylos et al. [1] seem to be reliable and the cause might already be discovered, taking us to the dimension of Aristotle's concept of "techné".

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