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Review

The neuronal influence on tumor progression

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ABSTRACT

Nerve fibers accompany blood and lymphatic vessels all over the body. An extensive amount of knowledge has been obtained with regard to tumor angiogenesis and tumor lymphangiogenesis, yet little is known about the potential biological effects of "neoneurogenesis". Cancer cells can exploit the advantage of the factors released by the nerve fibers to generate a positive microenvironment for cell survival and proliferation. At the same time, they can stimulate the formation of neurites by secreting neurotrophic factors and axon guidance molecules. The neuronal influence on the biology of a neoplasm was initially described several decades ago. Since then, an increasing amount of experimental evidence strongly suggests the existence of reciprocal interactions between cancer cells and nerves in humans. Moreover, researchers have been able to demonstrate a crosstalk between cancer cells and nerve fibers as a strategy for survival. Despite all these evidence, a lot remains to be done in order to clarify the role of neurotransmitters, neuropeptides, and their associated receptor-initiated signaling pathways in the development and progression of cancer, and response to therapy. A global-wide characterization of the neurotransmitters or neuropeptides present in the tumor microenvironment would provide insights into the real biological influences of the neuronal tissue on tumor progression. This review is intended to discuss our current understanding of neurosignaling in cancer and its potential implications on cancer prevention and therapy. The review will focus on the soluble factors released by cancer cells and nerve endings, their biological effects and their potential relevance in the treatment of cancer.

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1. The nervous tissue in the context of tumor microenvironment

Tumor development, similar to what has been suggested for normal organ homeostasis, should be regarded as a result of constant mutual interactions between tumor cells and their surrounding microenvironment. The communication between the tumor cells and the microenvironment drives the process of tumor progression [1]. Normally, cancer starts as a confined disease, which if diagnosed early, can be treated effectively by surgical removal of the primary tumor. The invasion of cancer cells into surrounding tissues, resulting in the development of distant metastasis, is the dangerous following step. In fact, most of the cancer-related deaths are due to invasive tumor growth and the subsequent increase of life-threatening metastatic disease. Several cellular and soluble components of the tumor microenvironment influence tumor progression, including the cellular events related to the metastatic spread of the disease by modulation of the biological behavior of the cancer cells. Moreover, the tumor microenvironment is dynamically remodeled in parallel to the progression of the disease. The recruitment of different cellular component to the surrounding stroma will contribute to the creation of a milieu of soluble factors and will also enhance the formation of new blood and lymphatic vessels.

In the early seventies, Folkman et al. [2] showed for the first time the evidence for the ability of tumors to foster new blood vessels, a process called *neoangiogenesis*. From then on, substantial efforts have been invested to uncover the mechanisms of this process and to find new drugs able to limit the growth of a tumor by blocking its blood supply [3,4]. The neovascularization of a tumor strongly influences cancer progression, and actively contributes to the progression from a dormant *in situ* lesion to a lethally metastatic disease. Vascular endothelial growth factor A (VEGFA) and its receptor, VEGF receptor 2 (VEGFR2; also known as FLK1), have been demonstrated to play a pivotal role during this process. For this reason, several anti-angiogenic strategies aimed at inhibiting VEGFA and VEGFR2 signaling have been developed [5], although in some cases with disputed results [6]. At present, VEGF-based therapies can increase the survival in cancer patients only by months rather than years [7].

Another endothelial network, essential for tissue homeostasis in the healthy individuals and a source of pathogenesis in different diseases including cancer, is the lymphatic vasculature [8–10]. The creation of new lymphatic vessels within the tumors, or *lymphangiogenesis*, contributes to the early spread of cancer cells. For example, it has been demonstrated that lymphoangiogenic factors influence the metastatic disease [11]. Discrimination between blood and lymphatic vessels has been a bit problematic in the past because of the shortage of lymphatic endothelium specific markers. During the last few years, the introduction of lymphatic markers such as LYVE-1 and podoplanin, has been a critical step in the right direction [11] helping to improve the clinico-pathological analyses of lymphangiogenesis in human cancer. In addition to showing that lymphangiogenesis is a process related to human cancer onset, these studies have also shown that expression of VEGF-C or VEGF-D is associated with lymph node metastasis in several human tumor types, further highlighting the importance of these growth factors for tumor spread [10,12].

Similar to the processes of neoformation of blood and lymphatic vessels, several evidence point out to the possibility of the formation of new nerve endings inside the tumors. The capacity of the tumors to stimulate their own innervation in a way similar to neoangiogenesis and lymphangiogenesis has been termed *neoneurogenesis*. Although the presence of nerve endings within the tumors has been described for bladder [13], eye [14,15], prostate [16], breast [17,18], pancreatic [19] and colon cancer [20], and others [15,21], the neoformation of axon within human tumors has only been described in prostate cancer [22]. Independent of the formation of new nerve endings or axons from the preexisting ones, there is an increasing body of research suggesting that the neuropeptides and neurotransmitters present in the tumor microenvironment play an important role influencing the course of the disease.

The role of the nerve fibers in the tumors was initially thought to be mechanical, behaving as “paths” that allows the migration of the perineural invading cells. However, now it has been suggested that the nervous system is in fact functionally relevant, modulating a complex network of mediators related to tumor progression. For example, the suppression of the immune response in cancer has been linked to the presence of neurotransmitters [23], and tumor vascularization and changes in vessel density have been shown to be affected by several neurotransmitters [24,25]. Moreover, cells respond to neurotransmitters increasing their migratory activity [26,27] and the presence of nerve fibers within the tumors correlates with a poorer clinical outcome [28] (Fig. 1). In addition, the interaction between the nervous system and the tumors seems to be reciprocal, since cancer cells are also able to secrete neurogenic factors [29–31] and axon guidance molecules [32], therefore stimulating and driving the ingrowth of new nerve endings to the tumor.

2. Presence and neoformation of nerve structures within the tumors

The cross talk between cancer cells and nerve fibers implies that both counterparts secrete factors that favor the rapid growth of both, making the neural-epithelial interaction a mutually beneficial process. Thus, it is likely that the perineural space is enriched in soluble factors that attract cancer cells favoring the process of perineural invasion. On the other hand, cancer cells secrete neurogenic and axon guidance molecules that would promote neurogenesis and the growth of nerve endings that will infiltrate the tumor.

2.1. Perineural invasion

Although there is no consensus about the process of perineural invasion (PNI), Batsakis offered the first definition of PNI as tumor cell invasion *in*, *around*, *and through* the nerves [33]. Since the idea of the presence of cancer cells around the nerves was controversial, this definition was later modified to propose that at least 33% of the circumference of a nerve should be surrounded by tumor cells to be referred to as PNI; anything less than 33% of tumor cells surrounding a nerve is therefore not considered invasion (reviewed in [34]). Initially, the observation PNI was thought to be cancer cells traveling through the lymphatic vessels located within the nerve. However, it was subsequently demonstrated that the perineural space is devoid of lymphatic vessels and thus, PNI is a true physical phenomenon [35] (Fig. 2).

The incidence and clinical significance of PNI has also been controversial, although in the majority of cancers it is associated with a poorer clinical outcome [34] and in some of them its measure can be used as an independent prognostic factor [36]. There are different biological consequences of PNI that affect tumor progression. Besides the use of nerve fibers as physical support for migration, the perineural