Biochimica et Biophysica Acta 1816 (2011) 105–118

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

The neuronal influence on tumor progression

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ARTICLE INFO

Article history:
Received 6 February 2011
Received in revised form 28 April 2011
Accepted 29 April 2011
Available online 14 May 2011

Keywords:
Neoneurogenesis
Neurotransmitters
Neuropeptides
Axon guidance molecules
Neurotrophic factors
Cancer progression
Perineural invasion

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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doi:10.1016/j.bbcan.2011.04.005

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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

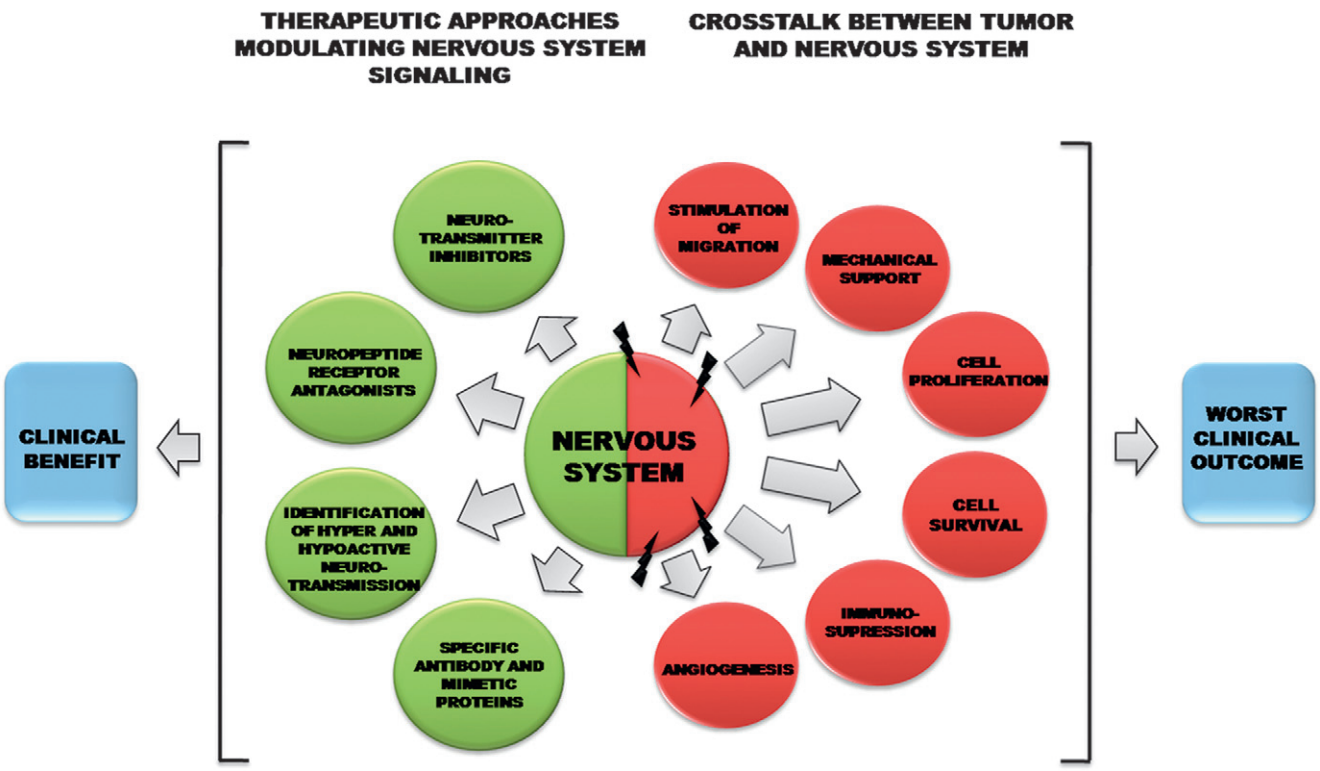

Fig. 1. Representation of the therapeutic approaches targeting the nervous system and the mechanisms influenced during cancer progression. The signals released by the nervous system can affect multiple pathways that will finally drive tumor progression and a poorer clinical outcome for the cancer patient. Several different therapeutic approaches to improve patient prognosis are under investigation.

environment is enriched for nerve-derived factors that constitute a protective niche for the cancer cells. This is nicely illustrated by the fact that prostate and pancreatic cancer cells are more proliferative and have decreased apoptosis when located in close proximity to a nerve space [37,38]. In such environment, cancer cells can exploit the advantage of the factors released by the nerve fibers that create a positive microenvironment for survival and proliferation. Besides, proinvasive signals are released within the peripheral nerve milieu influencing cancer cell migration (Fig. 2). Moreover, the formation of new axons could be a consequence of PNI, since cancer cells synthesize and secrete neurotrophic factors like NGF [29] and axon guidance molecules like netrin-1 [39].

2.2. Neoneurogenesis

2.2.1. Experimental evidences of axonogenesis in cancer

Besides invading peripheral nerves and using them for migration, it has been proposed that cancer cells stimulate their own innervations. Thus, the concept of neoneurogenesis includes the development of nerve endings (axons) towards the tumor. Cancer cells are able to secrete neurite outgrowth-promoting molecules and axon guidance molecules (see Sections 2.2.3 and 2.2.4) that would stimulate and drive the growth of these new axons to particular areas of the tumor.

Several *in vitro* approaches suggest the existence of such mechanism. The formation of the nervous system depends on the precise mechanism of chemotactic axon guidance induced by molecular gradients [40,41] and supported by extracellular matrix components [42,43]. Extracellular matrix components like the ones included in Matrigel support the axonal growth from explants of peripheral nerve-dorsal root ganglia (DRGs) obtained from the lumbar spinal cord of mouse embryos at 17 weeks of gestation [44]. A co-culture system with DRGs and cancer cells has been successfully used to estimate neurite outgrowth, its directionality towards cancer cells, and the existence of cancer cell-nerve interaction, migration of cancer cells towards and through the nerves (PNI) and the growth rate of cancer cells. Using this system, Ayala and collaborators have shown the directional outgrowth of neurites from the DRGs toward human cancer cells *in vitro* in prostate [22] and pancreatic cancer [38], providing support for the idea of the process of neoneurogenesis in human cancers.

2.2.2. Potential mechanism of axonogenesis in tumors

Although the stimulation of neoneurogenesis by tumor-released soluble factors has not been demonstrated in human tumors, it is likely that the system used by cancer cells to induce neurite outgrowth could be similar to the process of nerve recovery after injury. In contrast with the central nervous system (CNS), the peripheral nervous system (PNS) can support long-axon regeneration after injury. In the adult PNS, the Schwan cells produce several growth factors that can support axonal regeneration, including NGF, BDGF, IGF, CNTF and others [45]. Moreover, for a successful axon growth and elongation towards a target field, neurons depend on the activation of different signaling pathways shared by cancer cells. For instance, the protein Akt is important for neuronal polarity; GSK3 activity is related to microtubule stability and remodeling; and the PI3K family of proteins regulates cell polarity, motility and chemotaxis during axon specification [46]. Several of the growth factors secreted by the Schwan cells during axon regeneration are also secreted by cancer cells, along with other soluble factors that are able to activate the aforementioned signaling pathways in cells expressing their receptors. Thus, it is possible that within the tumor microenvironment, axonogenesis could be under the control of the cancer-derived signaling pathways similar to injury-induced axonal regeneration. We also have to consider another particularity of cancer cells, like the generation of their own extracellular matrix that would also support axonal growth [44]. In agreement with this concept, neurite outgrowth on muscle cell surfaces is also dependent on ECM molecules [47]. Despite the axonal ingrowth into the tumor, we cannot rule out the possibility of neogenesis of neuronal cells. Some

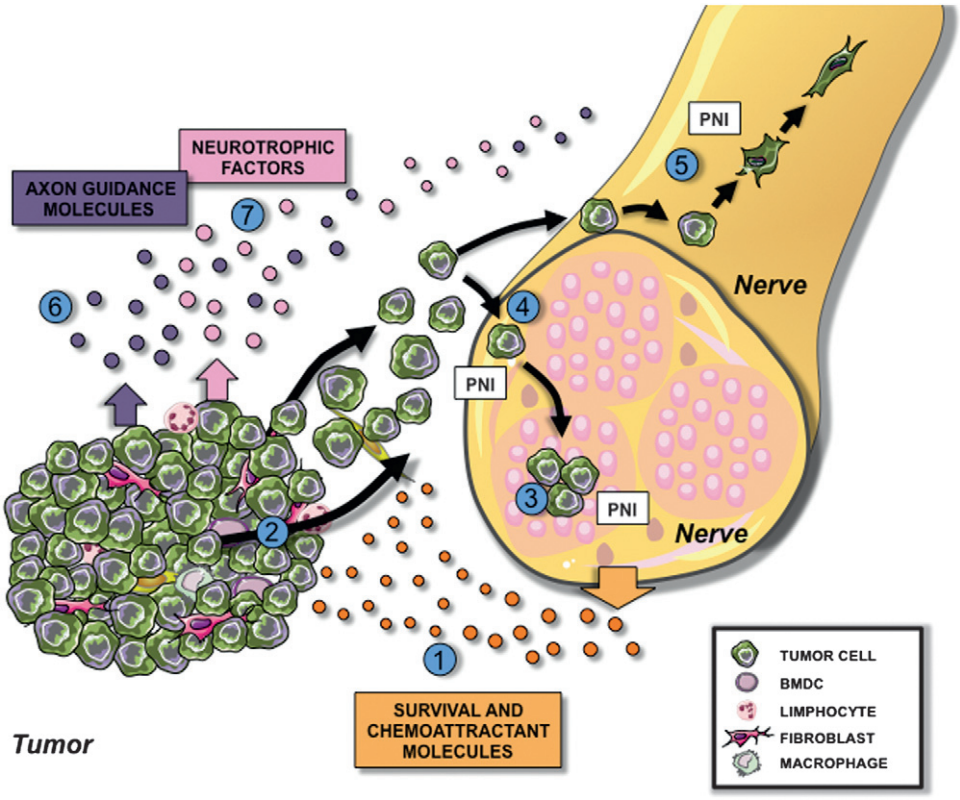

Fig. 2. Representation of the proposed reciprocal interaction between the nervous system and the tumor. 1. The nerves can secrete a milieu of factors that will promote cancer cell survival, proliferation and 2. migration toward the nerve. Once in the proximity of the nerve area, tumor cells will found a low-resistant barrier, being able to either migrate through the nerve or infiltrate it through 3. the endoneurium and 4. the epineurium. These different mechanisms will allow tumor cells to 5. migrate to distant sites. On the other hand, tumor cell will secrete both 6. axon guidance molecules and 7. neurotrophic factors that would influence neurite outgrowth towards the tumor. *This image has been created thanks to Servier Medical Art.* Adapted from [34]. PNI, perineural invasion; BMDC, bone marrow-derived cell.

authors have provided evidence that mesenchymal stem cells (MSC), a bone-marrow derived population usually recruited by tumor cells, were able to differentiate into functional neurons upon the activation of the correct differentiation pathways (reviewed in [48]). Recently, the transdifferentiation of cancer cells into functional endothelial cells has been reported [49], demonstrating how far tumors can go to create the most advantageous microenvironment for their progression.

2.2.3. Cancer-related neurotrophic factors

One of the several evidence supporting the idea that cancer cells can support the neoneurogenesis process is the fact that tumors can secrete several neuronal growth factors and axon guidance molecules. It is interesting to note that most of the factors known to induce neurogenesis, like NGF, BDNF, FGF or IGF-II [40] are usually secreted by tumors with bad prognosis and these factors exert autocrine or paracrine effects in the cancer cells. The creation of such a microenvironment by cancer and nerve-secreted factors will favor the progression of the disease by potentiating both the growth of the cancer cells and the neurites.

The family of neurotrophic factors can be subdivided into Neurotrophins, Neuropoietins, Insulin-like Growth Factors, Transforming Growth Factors and Fibroblast Growth Factors among others (Table 1). Neurotrophins display neurite-outgrowth-inducing and survival-promoting effects on neuronal cells. Some of the most relevant neurotrophic factors in cancer are discussed below.

2.2.3.1. Nerve growth factor. Nerve growth factor (NGF) was the first isolated neurotrophin and is well known for its role in nervous system development. A major biological function of NGF is the maintenance and survival of post-mitotic neurons, which makes it a strong candidate for the treatment of neurodegenerative diseases. In addition to its role in the development and maintenance of neuronal cells, NGF has significant effects on non-neuronal cells and during the process of tumorigenesis.

NGF has been related to cancer progression in several tumor types [50]. It is secreted by breast cancer cells but not by normal breast epithelial cells [29], and the treatment directed against NGF decreases breast cancer cell proliferation with a concomitant increase in apoptosis, and inhibition of tumor angiogenesis indicating that targeting of NGF is a potential therapeutic approach in breast cancer [51]. Prostate malignant epithelial cells also secrete NGF, which acts as an important autocrine factor for growth and metastasis. Interestingly, intravenous gammaglobulin (IVIg) contains natural antibodies against NGF. These antibodies inhibit growth and differentiation of the NGF-dependent prostate cancer cells demonstrating natural immunity to prostate cancer occurring in healthy individuals [52].

In a recent work using a mouse model of bone cancer pain, Mantyh et al. [53] observed that as the tumor progresses into the bone, there is nerve remodeling and a profuse sprouting of the sensory and sympathetic nerve fibers that induces pain in the animal. This mechanism was mediated by the presence of NGF in the tumor microenvironment and was reverted by the addition of anti-NGF [53] or by the treatment with the Trk inhibitor ARRY-470 [54].

2.2.3.2. Brain-derived nerve growth factor. Brain-derived neurotrophic factor (BDNF) is widely expressed in the brain, predominantly in the hippocampus, cortex, and synapses of the basal forebrain [55]. Existing data indicate that BDNF supports the long-term survival, differentiation, and synaptic activity of neurons [55,56]. In patients affected by Alzheimer's disease the mRNA levels of BDNF in the hippocampus and

Table 1
Summary of the neurotrophic factors family members and their receptors.

Family	Member	Signaling receptor
Neurotrophins	Nerve growth factor (NGF)	TrkA
	Brain-derived neurotrophic factor (BDNF)	TrkB
	Novel neurotrophin-1	gp130
	Neurotrophin-3 (NT-3)	TrkC > TrkA and TrkB
	Neurotrophin-4/5 (NT-4/5)	TrkB
Neuropoietins	Ciliary neurotrophic factor (CNTF)	CNTF receptor complex (CNTFRa, gp130, LIFRb subunits)
	Leukemia inhibitory factor (LIF or CDF/LIF)	LIF receptor complex (gp130, LIFRb subunits)
Insulin-like growth factor	Insulin-like growth factor-I (IGF-I)	IGF type I receptor (IGF1R) > insulin receptor (IR)
	Insulin-like growth factor-II (IGF-II)	IGF1R, less so IR
Transforming growth factor	Transforming growth factor α	TGFα receptor
	Transforming growth factor β (TGFβ1, TGFβ2, TGFβ3)	TGFβ type I, II and III receptors
GDNF ligands	Glial cell line-derived neurotrophic factor (GDNF)	GFRA2, GFRA1
	Neurturin (NTN)	GFRA2
	Persephin (PSP)	GFRα4
	Artemin (ARTN)	RET receptor, GFR-alpha 3 as co-receptor
Fibroblast growth factors	Acidic fibroblast growth factor (aFGF or FGF-1)	FGF receptors 1–4 (FGFR-1–4)
	Basic fibroblast growth factor (bFGF or FGF-2)	FGFR-1–3
	Fibroblast growth factor-5 (FGF-5)	FGFR-1, FGFR-2
Other growth factors	Transforming growth factor alpha (TGF-α)	EGFR
	Platelet-derived growth factor (PDGF: AA, AB and BB isoforms)	PDGF a- and b- receptors
	Stem cell factor (mast cell growth factor)	c-kit

in the temporal cortex are significantly decreased [57], suggesting a role for BDNF in preserving the integrity and function of cholinergic neurons and their target tissues. Moreover, BDNF and its high affinity receptor (tropomyosin receptor kinase B, TrkB) are expressed in several tumor types. For instance, in hepatocellular carcinoma patients both mRNA and protein levels of BDNF are highly expressed in the tumor compared to the undetectable levels in normal liver tissue [58]. Moreover, the serum levels of BDNF are correlated with the status of microsatellites and tumor recurrence, suggesting BDNF as a potential prognostic marker in hepatocellular carcinoma [58]. Using immunohistochemical techniques, high expression of BDNF and TrkB has been also observed in human prostate and bladder cancer, suggesting a predictive role in their diagnosis and/or management [59,60]. Recently, the selective Trk inhibitor AZ623 has been shown to inhibit BDNF-mediated neuroblastoma cell proliferation and signaling. Furthermore, treatment with AZ623 combined with topotecan resulted in the prolonged inhibition of tumor regrowth and a synergistic effect with topotecan [61].

2.2.3.3. Novel Neurotrophin-1. Novel neurotrophin-1 (NNT-1)/B cell-stimulating factor-3 (BSF-3), also reported as cardiotrophin-like cytokine (CLC), belongs to the interleukin 6 (IL-6)-family of cytokines [62,63]. Similar to IL-6, it exerts regulatory effects on normal B cell functions using the gp130 signaling subunit as a part of its receptor complexes [64]. The roles of NNT-1 in growth, survival, drug resistance, and migration have been examined within the bone marrow microenvironment of multiple myeloma (MM) cells suggesting potential utility of novel therapies targeting NNT-1 cascades [65].

2.2.3.4. Neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5). The neurotrophins (NT) family, along with NGF and BDNF, also includes neurotrophin 3 (NT-3) and neurotrophin 4/5 (NT-4/5). In addition, NT-3 and NT-4/5 share two classes of receptors with NGF and BDNF, the p75 neurotrophin receptor ($p75^{NTR}$) and the tyrosine kinase Trk receptors family (TrkA, TrkB, TrkC). Mainly, the signaling pathways activated by Trk tyrosine kinase receptors are involved in the regulation of survival and differentiation of neuronal cells [66]. However, recent studies investigating neurotrophin-mediated signaling in non-neuronal cells have demonstrated an involvement of the neurotrophins and their tyrosine kinase receptors in tumor growth and in progression of non-neuronal cancers. NT-3 is overexpressed in human pancreatic cancers [67], melanoma cells [68], medullar thyroid carcinoma [69], lung [31], pancreatic [70], prostatic [71] and ovarian carcinomas [72]. The overall view is that, as is the case with classic tyrosine kinase receptors, deregulation of kinase activities through various mechanisms generates survival signals via the PI3K/Akt and Ras/MEK/MAPK pathways, which in turn promote tumor progression [73]. These signaling events should be validated as therapeutic targets.

2.2.3.5. Transforming growth factors. Transforming growth factors (TGFs) are broadly accepted as a prototype of multifunctional growth factors and master switches essential for the regulation of several life-processes, such as development, repair, cell cycle control, differentiation, extracellular matrix formation, immune functions, angiogenesis, chemotaxis, and hematopoiesis [74–77]. The TGFs-superfamily includes several prominent members, including activins, bone morphogenetic proteins (BMPs), growth/differentiation factors (GDFs), and the glial cell line-derived neurotrophic factor (GDNF) subfamily associated with a common cysteine knot motif [78], also shared by other cytokines including the neurotrophins and platelet-derived growth factor (PDGF). Perturbations in TGFs signaling have been implicated in various human diseases, including cancer [79]. Indeed, during tumorigenesis TGFs secreted from tumor cells often lose their inhibitory function in favor of their oncogenic activity [80]. In humans, the overexpression of TGFs has been associated with breast, colon, esophageal, gastric, hepatocellular, lung and pancreatic cancer [81–83] correlating with tumor progression, metastasis, angiogenesis and poor prognostic outcome [81–83].

TGFs are also expressed in the nervous system carrying out several neural functions like key roles in the regulation of neuronal survival [84,85] and the orchestration of repair processes in the nervous system [86].

Current therapeutic approaches to modulate TGFs signaling involve antagonism of TGF-β ligand binding to the heteromeric receptor complex with isoform-selective antibodies, such as lerdelimumab (TGF-β_2) [87] and metelimumab (TGF-β_1) [88] or the pan-neutralizing antibody GC-1008 [89], and intracellular inhibition of the type I TGF-β receptor kinase with small-molecule inhibitors, such as LY550410, SB-505124 or SD-208 [90–92]. Alternatively, expression of TGF-β isoforms can be inhibited by antisense technology targeting mRNA for sequence-specific degradation [89]. In addition to the canonical SMAD signaling pathway downstream of the TGF-β type I receptor, TGF-β can also activate the JUN-N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK14; p38) pathways [93]. These SMAD-independent pathways provide different points of

therapeutic intervention that might be better at blocking TGF-β signaling.

2.2.3.6. Fibroblast growth factors. FGFs consist of a large cytokine family with several biological roles. Given the complexity of FGF signaling similar to TGFs, it is difficult to make generalizations about their role in development and differentiation. Fibroblast growth factors (FGFs) signaling through FGF receptors (FGFRs) affect fundamental developmental pathways, from mesoderm patterning in the early embryo [94] to the development of multiple organ systems [95]. As a consequence, any abnormalities in FGFs function lead to a variety of developmental defects [96] and/or growth of several cancers by directly driving cancer cell proliferation [97,98] and survival [99], and by supporting tumor angiogenesis [100,101]. FGFs are major determinants of neuronal survival both during development and during adulthood [102].

Several FGFRs tyrosine kinase inhibitors (TKIs) are currently in the early phases of clinical trials. Since FGFRs and VEGFRs share kinase domains with high structural similarity, several of FGFRs TKIs also inhibit VEGFRs (for example, TKI258 [103], BIBF 1120 [104], Brivanib [105] and E7080 [106]). This dual inhibition has the evident advantage of targeting two of the most important proangiogenic growth factors simultaneously. On the other hand, targeting multiple kinases might also amplify the side effects of these compounds. For these reasons, many laboratories are trying to develop therapeutic antibodies that are able to minimize the side effects of targeting FGFRs [107,108].

2.2.4. Axon guidance molecules in cancer

2.2.4.1. Netrins and their receptors. Netrins belong to a conserved family of secreted proteins having regional homology to laminins and are able to regulate axonal outgrowth [109–111]. The cellular expression of either receptors belonging to the DCC (deleted in colon cancer) or UNC5 families of Netrin-1 receptors determines the direction of Netrin-dependent neuronal outgrowth [112,113] (Table 2). DCC and UNC5 proteins are single-pass transmembrane receptors, with immunoglobulin domains. Moreover, UNC5 contains a thrombospondin type-I domain while DCC contains fibronectin type-3 domains [114]. The DCC receptors, which include the structurally similar Neogenin receptor, mediate neural attraction, while a complex of DCC and UNC5 receptor families is able to mediate repulsion [115,116]. Studies performed during the last years have found functioning Netrin molecules outside the nervous system (for example in the pancreas, intestine [117,118], lung [119], kidney, heart and vasculature [120,121]), suggesting their potential role in the development of these organs by affecting the migration of diverse types of cells.

In addition, regulation of the expression of Netrin-1 and its receptors may play a role in tumorigenesis. In fact, reduction in Netrin-1 expression has been detected in tumors of the prostate and the nervous system [122,123]. In cancers of the brain, stomach, pancreas, colorectal and testicle, low levels of somatic mutations of DCC have been detected [39]. Exogenous soluble Netrin-1 is able to reduce migration and induce increased levels of markers of early neuro-ectodermal differentiation in embryonic carcinoma cells suggesting a potential role for Netrin-1 in the regulation of differentiation in human embryonic carcinoma cells [124,125]. Netrin-1 and Neogenin have also been found in the mammary gland terminal end-buds that are implicated in maintaining adhesion between cap cells and luminal cells [126]. Overexpression of Netrin-1 has been observed in a large fraction of human metastatic breast tumors conferring a selective advantage for tumor cell survival and thus it could be a potential target for alternative anticancer therapeutic strategies [127].

Table 2
Summary of some axon guidance molecules and their receptors known to be related with tumor progression.

Family	Member	Signaling receptor
Netrins	Netrin-1	Deleted in colorectal cancer (DCC), Uncoordinated-5 (UNC-5)
	Netrin-3/NTNL2	Deleted in colorectal cancer (DCC), Uncoordinated-5 (UNC-5)
	Netrin-4/β	Deleted in colorectal cancer (DCC), Uncoordinated-5 (UNC-5)
	Netrin-G	Deleted in colorectal cancer (DCC), Uncoordinated-5 (UNC-5)
Ephrins	Ephrin A ligand	EphA receptor
	Ephrin B ligand	EphB receptor
Semaphorins	Semaphorins 1–7	Plexins, Neuropilins
Slit	Slit 1–3	Roundabout 1–4 (ROBO 1–4)

2.2.4.2. Eph/Ephrin. The Eph receptors (Table 2) form the biggest subgroup of the receptor tyrosine kinase (RTK) family. Eph receptors and their ephrin ligands have been implicated in diverse developmental and neurological functions, including hindbrain development in vertebrates and tissue patterning [128,129]. In addition, a variety of other biological activities are modeled through Eph/ephrin, including cell–cell interaction, cell migration, and increase in tumor growth, survival and metastatis. Increased Eph/ephrin signaling pathway activation has been shown to be associated with angiogenesis in several human cancers, including breast [130], lung [131], prostate [132] cancers, melanoma [133], and leukemia [134]. All these findings have been used to further advance novel cancer treatment methods. EphA2 (an Eph receptor) can be targeted by an antibody in aggressive lung tumors [135]. Another therapeutic approach could be the use of mimetic peptides that are able to target the ligand-binding domain of EphA2, and thus competing with ephrin ligands for binding [136,137].

2.2.4.3. Semaphorins. Originally described as axon guidance molecules influencing the development of the central nervous system [138], semaphorins and their receptors have also been found to be released by several types of cancer cells [139–141] and by cells in the tumor microenvironment [142] establishing their own autocrine regulatory loops to enhance cell survival. Unfortunately, our knowledge of semaphorins versatile signaling pathways is still lacking, and further studies on the semaphorins-mediated crosstalk between tumor cells and tumor stroma are needed. Developing ways to interfere with semaphorin-mediated signals might be a promising anti-cancer strategy.

3. Neurotransmitters and neuropeptides in cancer

Although several neurotrophic factors, axon guidance molecules, neuropeptides and neurotransmitters have been identified as mediators of the tumor-nerve interaction, the complex network of factors released as consequence of this interaction is largely unknown. A wide comprehensive characterization of both the soluble factors and their receptors expressed by cancer cells, or even by the cellular compartment of the tumor microenvironment, and related to tumor progression and metastasis will generate a new area for target discovery and therapeutic intervention.

To this date, several neurotransmitters and neuropeptides have been related to tumor progression mainly by stimulating the migration ability of cancer cells, a key event in the dissemination of tumor cells to distant sites. In the following section, we will describe some of the neurotransmitters and neuropeptides related to tumor progression (summarized in Tables 3 and 4), and we will discuss the possibility of their inhibition as a potential therapy. Although by themselves, most of these factors might not be essential for tumor cell survival, they have been shown to promote tumor growth and affect

Table 3
Summary of the most relevant neurotransmitters related to tumor progression.

Family	Member	Signaling receptor
Amino acids	Aspartate	NMDA receptor
	Glutamate (Glutamic acid)	Metabotropic glutamate receptor, NMDA receptor, Kainate receptor, AMPA receptor
	Gamma-aminobutyric acid	GABAB receptor, GABAA, GABAA-ρ receptor
	Glycine	Glycine receptor
Acetylcholine	Acetylcholine	Muscarinic acetylcholine receptor, Nicotinic acetylcholine receptor
Monoamine (Phe/Tyr)	Dopamine	Dopamine 1–5 (D1–5) receptors
	Norepinephrine (noradrenaline)	α-β Adrenergic receptors
	Epinephrine (adrenaline)	α-β Adrenergic receptors
Monoamine (Trp)	Serotonin (5-hydroxytryptamine)	5-HT1-7 receptors
	Melatonin	MTNR1 A–B–C receptors
Monoamine (His)	Histamine	H 1–4 receptors

the chemotherapeutic response of cancer cells. Therefore, since neurotransmitters and neuropeptides can activate signaling pathways related to cell proliferation and survival, including the PI3K, MAPK and Akt pathways [143], their inhibition should sensitize the tumors to the current chemo- or targeted therapies. Moreover, in some particular cases cancer cells can be influenced on their hormone dependency, since some cancer cells lost their dependence on growth factors when they are located in the proximity of a perineural space [144].

3.1. Classification of neurotransmitters and neuropeptides

Searching for the *nervous system* (specifically the *autonomous nervous system*) in the Pubmed or any science web in general, it is very common to find its classical description as divided into two opposed branches able to regulate autonomic functions of organs and tissues that are not under the central control: the sympathetic and the parasympathetic nervous system. The products of these systems are mainly 1) molecular messengers able to regulate multiple functions in the central and periphery nervous system, 2) potent cellular growth factor for normal cells, and 3) deep-seated signaling peptides in autocrine/paracrine stimulation, proliferation and migration of tumor cells.

The total number of neurotransmitters is not known, but is likely over 100 [145]. Despite this diversity, these agents can be classified into two large categories: neuropeptides and small-molecule neurotransmitters. Neuropeptides are transmitter molecules composed of 3 to 36 amino acids. Individual amino acids, such as glutamate and GABA, as well as acetylcholine, serotonin and histamine, are much smaller than neuropeptides and are therefore called neurotransmitters. In general, as a consequence of differences in the rate of transmitter release, neurotransmitters mediate rapid reaction, whereas neuropeptides tend to modulate slower functions [27].

The standard set of criteria used to corroborate that the supposed molecule is indeed a NT/neuropeptides at a given synapse are: 1) The substance must be present within the pre-synaptic neuron, 2) Specific receptors for the substance must be present on the post-synaptic cell and, 3) The substance must be secreted as a consequence of pre-synaptic depolarization, which must occur in a Ca^{2+}-dependent manner.

3.2. Most common neurotransmitters in cancer

The cancer incidence and progression seem to be strongly dependent on psychosocial factors [146]. Stress-related situations can induce the release of neurotransmitters and/or hormones that will further influence tumor onset, development and progression [24,147].

3.2.1. Epinephrine and norepinephrine

Catecholamines, also known as *stress-neurohormones* (or *stress-mediators*) due to their increased concentration in response to stressful events [148], are the most studied neurotransmitters for their role in carcinogenesis and tumor progression. Catecholamines are derived from the amino acid tyrosine. Epinephrine and norepinephrine, secreted mainly from the adrenal medulla and the sympathetic nerves,

Table 4
Summary of the most relevant neuropeptides related to tumor progression.

Family	Member	Signaling receptor
Neurohypophyseals	Vasopressin	Vasopressin receptor
	Oxytocin	Oxytocin receptor
	Neurophysin I	?
	Neurophysin II	?
Neuropeptide Y	Neuropeptide Y	Neuropeptide Y receptors NPY1R, NPY2R, PPYR1, NPY5R
	Pancreatic polypeptide	PPYR1
	Peptide YY	NPY2R
Corticotropin-releasing factor	Corticotropin (adrenocorticotropic hormone)	Corticotropin receptor
Opioids	Dynorphin	κ-opioid receptors
	Endorphin	μ1 opioid receptor >μ2 and δ opioid receptors >κ1 opioid receptors
	Enkephaline	Enkephaline receptors
	Secretin	Secretin receptor
	Motilin	Motilin receptor
Secretins	Glucagon	Glucagon receptor
	Vasoactive intestinal peptide	Vasoactive intestinal peptide receptor
	Growth hormone-releasing factor	Growth hormone-releasing factor receptor
Somatostatins	Somatostatin	Somatostatin receptor
Tachykinins	Substance P	NK1>NK2>NK3
	Neurokinin A	NK2>NK3>NK1
	Neurokinin B	NK3>NK2>NK1
Other neuropeptides	Bombesin	BB 1–4
	Gastrin releasing peptide	BB 2

respectively, are the most common representatives of this family. Recently, epinephrine and norepinephrine releases have been linked with stress-induced tumor-growth and progression. In fact, that these neurotransmitters can directly modulate several mechanisms related to tumor progression, such as cell proliferation, survival, and migration. In ovarian cancer cells, epinephrine and norepinephrine can modulate cell proliferation, survival and tumor angiogenesis through the activation of the β-adrenergic receptor (βAR)– cyclic AMP (cAMP)– protein kinase A (PKA) pathway [24,149]. βAR activation has been shown to increase metastasis formation in breast, lung and colon cancer models [150–152], and to accelerate growth in mammary tumors [153,154]. The use of β-blockers has been proven efficient in almost all the studies to overcome the pro-metastatic effects of βAR activation.

There are several mechanisms underlying the promotion of metastasis by epinephrine and norepinephrine. In a recent study, the activation of the β-adrenergic signaling in an orthotopic breast cancer mouse model of stress-induced neuroendocrine activation induced a 30-fold increase in the metastasis formation. This was accompanied by an increased recruitment of macrophages into the primary tumor site [155]. In other systems, these neurotransmitters have been reported to facilitate the angiogenic switch and to induce the secretion of VEGF and IL-6 by cancer cells [24,156,157].

From the prevention and therapeutic point of view, it is interesting to consider the potential role of cathecolamines in stress-induced cancer development. In addition to their role in tumor progression, their physiological concentrations related to stress situations or depression can favor the initiation of cancer [149,158]. Moreover, propranolol, a β-blocker, was shown to have preventive effects in the development of pancreatic ductal adenocarcinoma in mice [159], supporting the role of the catecholaminergic system in cancer development.

3.2.2. Dopamine

The effects of the catecholamine neurotransmitter dopamine on tumor growth are opposite to that of norepinephrine and epinephrine. Dopamine exerts antagonic effects on cell growth in normal and cancer cells; it promotes proliferation of non-transformed cells but has antiproliferative effects in cancer cells. In gastric cancer cells, dopamine inhibits IGF-1-induced proliferation by up-regulating the cell cycle regulator KLF4 [160]. The administration of dopamine has also been linked to growth diminution in several tumors models, such as stomach, breast and colon cancer [161,162]. Dopamine has been shown to inhibit VEGF–induced angiogenesis and to decrease the mobilization of endothelial progenitors from the bone marrow [162,163]. Most importantly, dopamine has shown significant synergism with conventional anticancer drugs, like doxorubicin or 5-fluorouracil (5-FU) [162].

Despite the anti-tumor effects of dopamine, there is controversy about the lack of its expression and cancer development [164,165]. Dopamine is a well-known inhibitor of prolactin, a growth factor for cancer cells. Thus, dopamine inhibition could promote tumor growth by increase in prolactin levels, as has been suggested for breast cancer [166,167]. However, there is no clear consensus about the role of the dopaminergic system in cancer development, and more epidemiological data is needed in order to get a broader picture of dopamine and cancer risk.

3.2.3. Serotonin

Serotonin is a neurotransmitter and serves critical cognitive and behavioral functions in humans, with numerous important peripheral functions in the gut, vasculature, immune system, and at wound sites [168–170]. Serotonin is well known for its role as a neurotransmitter involved with mood regulation; but it also has a role in normal mammary gland development, where it helps to regulate lactation and involution influencing the mechanisms of homeostasis in the mammary epithelium [171,172]. Deregulation of these epithelial homeostatic systems is in part responsible for breast cancer onset: breast cancer cell lines show significantly elevated tryptophan hydroxylase 1 (TPH1; a serotonin receptor) transcript and protein levels. Since TPH1 is rate limiting factor for serotonin synthesis in mammary epithelial cells, as well as other systems [173], breast cancer cells synthesize excess serotonin, which they then employ to sustain their growth advantages [174].

Regulation of epithelial homeostasis by serotonin is not restricted to the mammary epithelium. In fact, serotonin has also been implicated in epithelial homeostasis of the lung, pancreas, liver and prostate [175–178]. Therefore, variation in local serotonin signaling may be a common mark of cancer progression in epithelial tumors.

New therapeutic approaches modulating serotonin signaling are under investigation; for example, Keyhole limpet Hemocyanin (KLH), a copper-containing respiratory pigment found in the mollusk, *Megathuracrenulata*, that targets the serotonergic signaling pathway has been shown to inhibit cellular proliferation in human cancer cell lines of the breast, esophagus, pancreas, and prostate [179]. Moreover, three drugs in wide use to treat thought disorders — paliperidone, pimozide and risperidone that are potent and well-tolerated inhibitors at serotonin receptor 7, are under investigation for growth factor deprivation in an adjunctive role in glioblastoma treatment [180].

3.2.4. Acetylcholine

Acetylcholine is the neurotransmitter of the parasympathetic system and its biological activity is mediated by nicotinic and muscarinic acetylcholine receptors (n-AchR and m-AchR, respectively) in the central and peripheral nervous system [181]. The n-AchR is a Ca^{2+} or Na^{+} ion channel whereas the m-AchR belongs to the family of G-protein coupled receptors with seven transmembrane spanning domains.

Acetylcholine is one of the most important neurotransmitters implicated for pharmacotherapy. Its rapid inactivation is facilitated by the cholinesterase enzymatic cleavage, which is critical in synapses with very high repetition rates such as the neuro-muscular junction in skeletal muscle. However, it is also implicated in slower synaptic activity in the peripheral autonomic nervous system, as well as in the central nervous system. In 1989, for the first time Schuller and coworkers [182] suggested the potential role of the autonomic nervous system in the regulation of cancer cells. They showed that nicotine as well as 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK; a tobacco-specific nitrosamine) stimulated the proliferation of human small cell lung cancer (SCLC) cells via binding to n-AChRs, and the selective agonist for βARs, isoproterenol, stimulated the growth of the human lung adenocarcinoma cells [182].

In recent years, n-AChRs have been identified as important regulators of several other cancer types. In fact, activation of this pathway has been shown to induce the growth of mesothelioma cells (also displaying anti-apoptotic effects) [183]; to induce the proliferation of colon cancer cells [184]; and to stimulate the proliferation, angiogenesis, and cell migration of gastric cancer cells as a consequence of nicotine-induced prostaglandin E_2 activity, cyclooxigenase-2 (COX-2), and VEGF augmentation [185].

The m-AChRs, the other acetylcholine family receptors, are also expressed in most SCLC and many non-small cell lung carcinomas (NSCLC) [186]. A growth-promoting effect of m-AChRs, mediated by transactivation of EGFR and subsequent activation of ERK, has been demonstrated in colon cancer cells [187]. Activation of the MAP kinase by m-AChRs induces cell proliferation and protein synthesis in human breast cancer cells [188].

For these reasons, the potential therapeutic effects of both the nicotinic and muscarinic receptor antagonists are under investigation. For example, NSCLC cells express n-AChRs and the activation of these receptors by agonists, namely nicotine, inhibits apoptosis, whereas receptor antagonists have a pro-apoptotic effect [189]. Some

muscarinic antagonists currently used in the treatment of genitourinary disease (e.g. darifenacin) have also been shown to have the ability to arrest tumor progression in nude mice [190]. The treatment of SCLC cells with M3R antagonists inhibited cell growth both *in vitro* and *in vivo*, and decreased MAPK phosphorylation in tumors in nude mice suggesting that M3R antagonists may be useful adjuvant for treatment of SCLC [191].

3.2.5. Glutamate

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system (CNS) [192]. It works through two classes of receptors: ionotropic glutamate receptors and metabotropic glutamate receptors. Based on their structural similarities, the ionotropic glutamate receptors are subdivided into three groups: AMPA, NMDA and Kainatereceptors. On the other hand, metabotropic glutamate (mGlu) receptors are G-protein coupled receptors (GPCRs) generally divided into subgroups (so far, eight members of mGluRs have been identified) based on sequence similarity, pharmacological and intracellular signaling mechanisms. In addition to the well-established role of the glutamaergic system in the CNS, emerging evidences point to a role for glutamate and its receptors in peripheral tissues [193,194] and in cancer [195,196]. In fact, the expressions of glutamate and glutamate receptor subunits have been found in several cancer cell lines and tumors, i.e., colorectal cancer [197,198], glioma [199–201] gastric cancer [202], prostate cancer [203], oral squamous cell carcinoma [204], melanoma [205,206] and osteosarcoma [196].

In the clinical setting, the expression of glutamate receptor could be used for prognostic purposes; it has been demonstrated that oral squamous cell carcinoma overexpresses the glutamate receptor, NMDAR1, and the up-regulation of NMDAR1 is well-correlated with the TN stage tumor size, presence of lymph node metastases and poorer survival [207]. In colorectal carcinoma, overexpression of mGluR4 is associated with poor prognosis [198]. And in colon cancer cell lines, elevated mGluR4 expression or activation by agonists promotes cell survival in the presence of 5-Fluorouracil (5-FU), whereas decreased mGluR4 expression or inactivation by antagonists leads to cell death, suggesting that the cancer cells overexpressing mGluR4 are protected against 5-FU cytotoxicity and becoming 5-FU resistant [197]. On the other hand, the expression of mGluR4 has been shown to be inversely correlated with tumor aggressiveness, spreading and recurrence in medulloblastoma [208], indicating a new role of glutamate and its receptor in tumor progression, thus showing that the clinical significance of glutamate receptor expression may be different among different tumors.

3.2.6. Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the central nervous system, where it has been shown to play a role in pathological conditions [209]. Mostly, GABA works with two classes of cellular receptors: (*a*) the ionotropic $GABA_A$ and $GABA_C$ receptors, which are oligomeric chloride channels [210,211] and (*b*) the metabotropic $GABA_B$ receptor. The $GABA_B$ receptor is a member of the serpentine or seven-helix receptor family and is related to the chemokine receptors and catecholaminergic receptors, both of which have been shown to be involved in the regulation of leukocyte and tumor cell migration [212].

Several reports have suggested a relationship between the GABAergic system and oncogenesis [213,214]. In pancreatic duct epithelial cells, all components of the stimulatory network (adenylyl cyclase-dependent intracellular signaling downstream of beta-adrenoreceptors (β-ARs)) are upregulated resulting in the release of epidermal growth factor, vascular endothelial growth factor and arachidonic acid. At the same time, GABA, which inhibits this pathway by blocking the activation of adenylyl cyclase, is suppressed [215]. Conversely, GABA content is increased in several types of human tumors such as colon, gastric, ovarian, and breast cancers [216–219]. $GABA_A$ receptor is upregulated in sporadic breast cancer [220] and pancreatic adenocarcinomas [221]. These findings suggest that increased GABA levels could reflect a local anti-tumor response. For these reasons the effect of GABA and its analogs, such as baclofen, on the growth of cancer are under investigation as potential new therapeutic target [222].

3.3. Neuropeptides in cancer: tachykinins

Neuropeptides are small polypeptides synthesized by several cell types in the soma on the rough endoplasmic reticulum (RER) as larger pro-peptide molecules that are post-translationally cleaved before they arrive at the Golgi apparatus. In the *trans*-Golgi network, the cleaved neuropeptides are packaged into secretory vesicles and transferred, via the so-called "fast axonal transport" to the presynaptic terminal. These signaling peptides play a crucial role in the regulation of exocrine and endocrine secretion, smooth muscle contraction, pain transmission, fluid homeostasis, blood pressure and inflammation. In addition to these traditional functions, neuropeptides can also act directly as potent cellular growth factors for multiple cell types [223] and could play an important role in cancer progression [26,27].

Neuropeptides function peripherally as paracrine and endocrine factors to regulate diverse physiologic processes and act as neurotransmitters or neuromodulators in the nervous system. In the large majority of cases, the receptors which mediate signaling by neuropeptides are members of the superfamily of G-protein-coupled receptors (GPCRs) [224]. In cancer, they can also act as autocrine and paracrine factors [225] regulating several processes related to tumor progression.

Several neuropeptides have been implicated in tumor progression, including bradikinin, colecistokinin, neuropeptide Y, and substance P. Substance P (SP) belongs to the tachykinin family, and is synthesized by macrophages, neuronal, endothelial, and epithelial cells [226]. Human tachykinins, including substance P (SP), neurokinin A and neurokinin B are codified by the *TAC*1, *TAC3* and *TAC4* genes, and interact with a family of G-protein coupled receptors (GPCRs), the tachykinin receptors NK1, NK2 and NK3, respectively [226]. SP is an undecapeptide involved in mediating several physiological processes including the process of wound healing where it facilitates the neurogenic inflammation and regulation of hematopoiesis [227,228]. Both SP and NK1 are overexpressed in several cancers including breast, ovarian, prostate, pancreas, thyroid and glioblastoma, among others [226].

In breast cancer, SP and its receptors are implicated in the acquisition of oncogenic properties and in the facilitation of bone marrow metastasis [229–232]. The activation of NK1 receptor by SP induces signaling pathways like PI3K, the NF-κB pathway, and mitogen-activated kinases (MAPKs), promoting the proliferation and survival of cancer cells. Given the relevance of SP-NK1 signaling in cancer, several efforts have been invested in developing therapeutic inhibitors against NK1 [233] or SP [234].

4. Neurosignaling in inflammation and cancer progression

After tissue injury, sensory nerves release neuropeptides that mediate neurogenic inflammation. Neuropeptides can orchestrate the wound healing process by modulating a network of mediators like the immune system cells. Moreover, neuropeptides like SP or CGRP act as potent mediators of neurogenic inflammation by increasing the vasculature permeability and favoring edema formation [235].

The release of neuropeptides in an injured tissue could serve as the initial signal to promote the recruitment of immune cells [236]. These cells, will in turn release cytokines that will induce the synthesis of neurotrophic factors necessary to stimulate neurite growth. This idea

is supported by the fact that nerve fibers cannot exist without a local control by growth factors. For instance, immune cells can synthesize neuropoeitic cytokines like IL-6 that can induce neuronal survival, differentiation and neurite outgrowth [143]. Experimental evidence also supports the role of SP in skin wound healing by inducing neurite outgrowth [237]. In fact, wound healing can be accelerated by the administration of sensory neuropeptides [238].

Despite inducing the recruitment of different immune system cells in an injured site, neuropeptides can also induce immunosuppression by heterologous desensitization of chemokine receptors. During heterologous sensitization, the activation of a given GPCR can induce the phosphorylation of the cytoplasmic tails of another GPCR, which then becomes insensitive to further signaling. Chemokine receptors present in immune cells have been shown to be heterologous inhibited by neuropeptides like opioids and VIP, contributing to immunosuppression [239].

Although inflammation after injury is related to tissue regeneration, several evidences support the idea that when the inflammation becomes chronic or is maintained for a long period of time, several pathological processes are activated. In fact, it is believed that chronic inflammation provides a favorable microenvironment to support cell transformation through the release of cytokines and growth factors that support epithelial growth. In this scenario, it is plausible that the factors released as a consequence of neurogenic inflammation could also provide a milieu of factors that would favor cell transformation [240].

5. Concluding remarks: the nervous system as a therapeutic target for cancer

Even though the true implication of the nervous system in cancer progression has begun to be elucidated only in the past few years, it is clear that a better understanding of how this reciprocal system operates will provide new insights for therapeutic intervention against cancer progression.

It is important to remark that the factors released by the nervous system as a consequence of the psychological and social pressures might lead to (or even enhance) cancer progression by changing the efficiency of the drugs used for the treatment of cancer. Since the factors released by nervous system in response to stress seem to have important influence on efficacy of drugs, it might be essential to revisit the method of testing the drugs *in vivo* that are currently performed using stabulated stress-free animals. Cancer handling using conventional treatments such as chemotherapy, or even surgical ablation, usually escape the difficulties added by nervous system and life-style factors coming from and regulated by tumor host environment. As a consequence, the initiation, progression and especially relapse of the most common human cancers, as we documented above, are strongly influenced by an imbalance between stimulatory and inhibitory nervous system factors. Following this line of thought, it seems quite naïve to challenge tumors only by blocking relevant cellular signaling molecules, such as tyrosine kinase, usually overexpressed in some cancer cells. A different approach, resembling the one involved with hormone-responsiveness, and that considers the identification of hyper and hypoactive neurotransmission in each patient seems to be necessary.

Several experimental evidences provide support for the use of neurotransmitter inhibitors or neuropeptide receptor antagonists for the treatment of cancer. For example, as discussed earlier, cancer-related bone pain is caused by the sprouting of sensory nerves within the bone, a process that can be reverted by the inhibition of NGF. Since inhibition of NGF has also been shown to have anti-tumorigenic effect, such therapies that prevent the reorganization of sensory nerve fibers in cancer could provide, not only a potential treatment against cancer but also a cure for neuropathic pain that accompanies it [240,241].

Acknowledgments

This work has been partially funded by a grant from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III (PI080022), by a grant from the Fundación Cellex, and by Redes Temáticas de Investigación en Cáncer (RTICC, RD07/0020/2014).

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