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Neural plasticity of the uterus: New targets for endometrial cancer?

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Abstract

Endometrial carcinoma is the most common gynecological malignancy in Western countries and is expected to increase in the following years because of the high index of obesity in the population. Recently, neural signaling has been recognized as part of the tumor microenvironment, playing an active role in tumor progression and invasion of different solid tumor types. The uterus stands out for the physiological plasticity of its peripheral nerves due to cyclic remodeling brought on by estrogen and progesterone hormones throughout the reproductive cycle. Therefore, a precise understanding of nerve-cancer crosstalk and the contribution of the organ-intrinsic neuroplasticity, mediated by estrogen and progesterone, of the uterine is urgently needed. The development of new and innovative medicines for patients with endometrial cancer would increase their quality of life and health. This review compiles information on the architecture and function of autonomous uterine neural innervations and the influence of hormone-dependent nerves in normal uterus and tumor progression. It also explores new therapeutic possibilities for endometrial cancer using these endocrine and neural advantages.

Keywords

autonomic nervous system, endometrial cancer, nerve-cancer, nerve plasticity, neuroreceptor, neurotherapy, neurotransmitter, sex hormones signaling

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Introduction

Nerve-cancer interaction was first described in the pain process associated with cancer progression[1] and perineural invasion (PNI), which cancer cells use as a track to disseminate.[2] Over recent decades, nerve-cancer crosstalk as a contributor to the tumor microenvironment has come to be seen as an important key-player. It is where activated downstream signaling pathways stimulate cancer cells to grow and migrate.[3]

Tumors interplay with nerves to stimulate and maintain nerve infiltration through a paracrine mechanism involving the secretion of growth factors driving to neurogenesis.[4] Reciprocally, cancer cells use nerves to activate angiogenesis and contribute to immune modulation and to tumor dissemination through the release of catecholamines like noradrenaline, epinephrine, dopamine, acetylcholine, and neurotrophic factors induced by cancer and stromal cells.[5,6]

The active crosstalk between nerves and tumor cells was first demonstrated in prostate[7] and gastric[8] cancers, and

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recently extended to other types of cancer. In cancer, the actions of the sympathetic and parasympathetic nervous systems seem complementary and not in opposition, a well-known and accepted relationship in human physiology.[3] For example, the sympathetic nerves stimulate the early stages of cancer progression while the parasympathetic nerves activate cancer cell dissemination at later stages.[7] Furthermore, it is known that the density of sympathetic and parasympathetic nerves infiltrating the microenvironment is greater in prostate, colorectal, and breast tumors. Moreover, it has been associated with tumor aggressiveness, poor clinical outcomes as well as decreased patient survival.[9–11]

Parallel to the prognostic relevance of endometrial cancer (EC), the therapeutic implication of neural control emerges as a new paradigm for treatment and cancer prevention. Denervation of the primary tumor by the destruction of both the sympathetic (adrenergic) and parasympathetic (cholinergic) nerves, surgically or pharmacologically, resulted in a significant decrease in cancer growth in experimental models of prostate, gastric, pancreatic cancers, and basal cell carcinomas.[7,8,12,13]

The morphology of the uterus is characterized by a physiological plasticity of the peripheral nerves due to its cyclical remodeling throughout the reproductive cycle under the influence of estrogen and progesterone.[14] As a consequence, understanding nerve-crosstalk in EC is a challenge considering the complex relationship between hormone levels and nerve plasticity. Among uterine cancers, endometrial carcinoma is the most common gynecological malignancy in Western countries, and its incidence rate is expected to increase due to a rise in the index of obesity along with prolonged life expectancy.[15] Despite the highest survival rate of all gynecological cancers, the survival rate is poor with only 15% of women surviving for 5 years when EC is diagnosed at the latest stage (IV).[16] Regarding the neural system as a recent and interesting cancer progression contributor, an understanding of the mechanisms could lead clinicians to uncovering interesting information for the prognosis and management of EC.

This review compiles information on the architecture and function of autonomous uterine neural innervations and the influence of hormone-dependent nerves in normal uterus and tumor progression. Furthermore, it explores strong and weak points and exposes new therapeutic possibilities for EC using these endocrine and neural advantages to be applied in the clinical management of this condition.

Autonomous innervation and nerve plasticity of the uterus

Sympathetic and parasympathetic nerves in the uterus

To interpret the relationship between uterine innervation and EC, it is relevant to understand the anatomy of the uterus and the physiological distribution of the fibers of the autonomic nervous system (Figure 1(a)). Macroscopically, the uterus can be divided into the body or corpus and the cervix. Laterally, it is connected to the ovaries by the fallopian tubes. The uterine corpus is composed of three main tissue layers. The endometrium is the inner lining that goes through morphologic and functional changes during the hormonal cycle. Two different stratums can be distinguished. The basal one that is adhered to the myometrium and the functional layer that proliferates and then sheds during the menstrual cycle. Moreover, the endometrium plays an important role during embryo implantation in pregnancy.[17] The second layer, the myometrium, is composed of smooth muscle cells (myocytes) distributed in longitudinal fibers in the outer position and circular or oblique fibers in the internal part. Finally, the outer layer is known as the serosa and is composed of epithelial cells. Regarding vascularization, arcuate vessels originating from anastomoses of uterine and ovarian vessels penetrate the myometrium in a spiral-shape and branch into radial arteries that traverse the myometrium to arrive at the endometrium as spiral arteries[18] (Figure 1(b)).

Sympathetic (SNS) and parasympathetic (PSNS) divisions of the autonomic nerve system are essential to connecting organs to the central nervous system (CNS).[19] Depending on the nature of the stimuli transmitted, autonomous innervation has both afferent and efferent components. The afferent component conducts somatic and visceral sensory stimuli from the periphery to the CNS, while the efferent component, also known as the motor branch, sends impulses to activate the smooth muscle, cardiac muscle, and glands.[20]

Anatomically, the sympathetic pre-ganglionic neurons innervating the uterus are in the intermediolateral cell column of the spinal cord at the T12-L2 level. Their pre-ganglionic fibers pass through the sympathetic chain, exit in the lumbar nerves, and synapse with the post-ganglionic neurons inside the inferior mesenteric ganglion. After that, the sympathetic fibers are carried into the pelvis as the right and left hypogastric nerves main trunks from the superior hypogastric plexus.[21] The post-ganglionic fibers from these neurons pass through the inferior hypogastric plexus. They interact with fibers from the PSNS and continue to the uterovaginal plexus to innervate the vagina and the uterus. In addition, distinct ganglia selectively innervate restricted areas of the uterus, thereby revealing region-specific control of uterine activity.[20] Finally, some pre-ganglionic fibers from the L1–L2 spinal segments directly descend in the sympathetic chain and synapse with post-ganglionic neurons in the hypogastric plexus (Figure 1(a)).

The parasympathetic pre-ganglionic neurons that innervate some locations of the female genital tract and the uterus are placed in the intermediolateral cell column of the sacral spinal cord at the S2–S4 level. Parasympathetic fibers exit from the ventral roots of the spinal medulla and travel through the pelvic splanchnic nerves. There, they

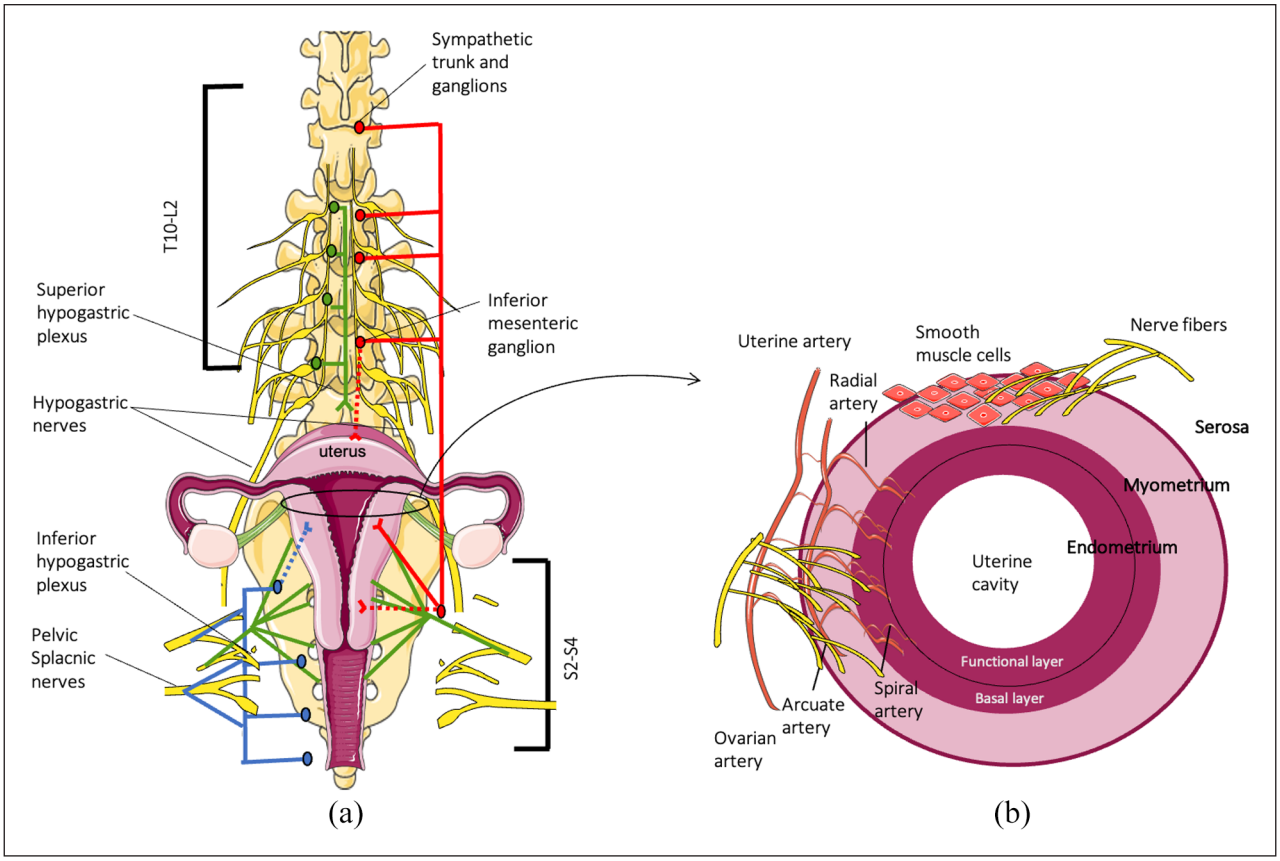

Figure 1. Autonomic innervation in the uterus: (a) Autonomic innervation distribution in the uterus. (b) Uterus anatomy: layers, nerves, and vessels. Neural control of the uterus is provided mutually by SNS and PSNS fibers creating a visceral co-regulation. The origin of SNS pre-ganglionic fibers initiates from the thoracolumbar region [T10-L2] of the CNS. SNS ganglia, where synapse is produced, are mainly located along the paravertebral sympathetic chain that runs parallel to the spinal cord. The post-ganglionic fibers finally join the spinal nerves to innervate the uterus. PSNS comes from the craniosacral region [S2–S4]. The PSNS ganglia and origin nerve roots are situated close to the uterus where shorter fibers make up the pelvic splanchnic nerves that innervate the uterus (a). Red: sympathetic nervous system; Blue: parasympathetic nervous system; Green: visceral afferents; Continuous line: pre-ganglionic fibers; Dotted lines: post-ganglionic fibers. In detail, uterine anatomy is composed of three layers and an exceptional vessel network that interacts with the autonomic nervous system (b).

pass through the inferior hypogastric plexus to reach the uterine tissue[20] (Figure 1(a)).

Topographically, the autonomic nerve fibers are heterogeneously distributed in the uterus, being higher in the tubal end of the uterine horn (endometrial junction) and in the cervix.[22] Within the different uterine layers, nerve density is moderate in the circular and longitudinal smooth muscle of the myometrium and abundant around the blood vessels of the arcuate and radial arteries in the vascular zone that is interposed between these two smooth muscle layers[23,24] (Figure 1(b)). Innervation in the non-pathological endometrium has not been studied extensively. According to initial literature,[14] this layer may be poorly innervated by autonomic fibers that would be located around the vessels and restricted to the basal layer. The most interesting available information comes from research into pathological situations like endometriosis. The presence of nerves in endometriotic tissue has been confirmed in humans and murine models where ectopic endometrium implants develop sympathetic, parasympathetic, and sensory nerve fibers.[25] Both layers of the endometrium of women with endometriosis appear to be densely innervated.[26] Nevertheless, the identification of nerve fibers in the functional layer of non-pathological endometrium is controversial, and it could be relationated with hormonal changes of reproductive cycle.[27]

Neurotransmitters and neuroreceptors of the autonomic nervous system in the uterus

In the sympathetic branch, the pre-ganglionic fibers release the neurotransmitter acetylcholine (ACh), which acts on cholinergic receptors on the post-ganglionic cells (Figure 1). These cells release mainly norepinephrine (NE) from sympathetic endings. Interestingly, sympathetic innervation in the uterus also makes up a complex system involving

Table 1. Neurotransmitters and their specific receptors in the neural control of uterine responses and endometrial cancer.

Neural signaling[a]	Healthy uterus			Endometrial cancer
	Endometrium	Myometrium	Endothelium	
	Endometrial cells	Myocytes	Endothelial cells	Endometrial tumor cells
Sympathetic	NE; β2 > β3 > β1; Epithelial proliferation[22,28,29]	NE; α1 > α2; Contraction[31,32] NE; β2 > β3 > β1; Tocolysis[31,32]	NE; α1 > α2; Vasoconstriction[22,28] NE; β1; Vasodilation[22,28]	NE; β2 > β3 > β1; Epithelial proliferation[33]
Parasympathetic	ACh; nAchR-α7; MMP-9 secretion[34]	ACh; M3 > M2; Contraction[34,35]	ACh; M3 > M1 > M2; Vasodilation[34]	ACh; M3 > M1 > M2;[35,36]
Dopaminergic	DA; DRD2;[37]	–	DA; DRD1 > DRD2; Antiangiogenic effect[37]	DA; DRD1 > DRD2; Antiangiogenic effect[38,39]

NE: noradrenaline; β: beta-adrenergic receptor; α: alpha-adrenergic receptor; Ach: acetylcholine; nAchR: nicotinic receptor; M: muscarinic receptor; DA: dopamine; DRD: dopamine receptor.
[a]Neurotransmitter; receptor(s) ordered by expression and relevance; action in the uterus.

several types of co-transmissions that consist of a whole range of other molecules belonging to the synaptic vesicles.[28] For example, NE along with adenosine triphosphate (ATP), chromogranin, hydroxylase, and other molecules with oxytocic and tocolytic effects are released from the sympathetic neurons through exocytosis.[29] These compounds decrease the release of neurotransmitters from local nerve endings and can modulate smooth muscle cell activity via interaction with specific receptors located on the membrane of the connective tissue cells, the endometrium, and the placenta.[30] The isthmic uterine muscle cells especially express type A α1 adrenergic receptors (α1AR) with a contractile effect,[31] whereas those from the uterine body mainly possess β2 adrenergic receptors (β2AR) that induce tocolysis. β1 and β3 adrenergic receptors (β1AR-β3AR) expression has also been described in myometrial cells, both with a tocolytic effect[32] (Table 1).

On the contrary, the uterine parasympathetic fibers mainly release ACh to modulate myometrial activity.[34] These cholinergic endings possess vesicles that contain ACh that is stored together with ATP and proteoglycans.[30] ACh stimulates muscarinic acetylcholine receptors (CHRs) on uterine myometrial cells. These receptors belong to the superfamily of G protein-coupled receptors, five CHMRs genes corresponding to subtypes M1, M2, M3, M4, and M5 receptors have been identified. CHRM3 has been described as the most expressed in the uterus and mainly mediates uterine contractions.[36] ACh administration induces an increase in the frequency and intensity of myometrial contractile waves through the M3 receptor with no significant change in tone. Although M3 receptors are present on the membrane of all myometrial cells, cholinergic endings are mainly distributed in the cervical area and the isthmus as well as the rest of the uterus in small numbers. Therefore, parasympathetic stimulation causes cervical and isthmic area muscle contraction with little or no effect on the uterine body[35] (Table 1).

Estrogen, progesterone, and uterine nerve plasticity

In a physiological endometrium environment, estrogen induces proliferation of the glandular epithelium, stroma, and vessels. Progesterone prepares the endometrium for implantation, by overcoming the proliferative effect of estrogen and inducing differentiation of the glands, stroma, and vessels.[40] Estrogen signaling is mediated by one of two receptors: estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ).[41] Progesterone signaling is mediated by the progesterone receptor (PR) of which two isoforms, PRA and PRB, have been identified.[42]

Another remarkable function of estrogen and progesterone is the capacity to remodel uterine innervation in response to their cyclic variations in circulating levels from puberty onward to menopause, inclusive of pregnancy.[14] The proportion of neurons expressing ERα is greater in the uterine-projecting neurons. That suggests that they are selectively sensitive to the effects of estrogen.[43] Sympathetic nerves are the most susceptible while parasympathetic and sensory nerves show no significant changes. Estrogen elicits a rapid degeneration of sympathetic terminal axons in the myometrium and, conversely, they regenerate under low-estrogen conditions.[44] Mechanistically, the myometrium produces proteins that repel sympathetic axons, including BDNF, neurotrimin, semaphorins, and pro-NGF, in the presence of the steroid hormone.[14] In addition, estrogen also affects neurotrophin receptor expression in sympathetic neurons, which favors the pro-degenerative effects of the target tissue.[44] It is also an important modulator of the release of NE from the

nerve terminals influencing the metabolism and turnover of its neurotransmitter and its synthetic enzyme activity.[14]

Concerning progesterone, it mediates neuronal plasticity by altering the expression patterns of the corresponding A and B receptors in some neurological diseases. However, its specific role in uterine nerve plasticity still remains uncertain.[45] As this hormone is especially linked to pregnancy, several authors that have used experimental models in induced pregnancy states have described modifications of NA levels[46] accompanied by a degeneration of uterine nerves.[47,48] These findings shine a light on the complexity of the neuroplasticity phenomenon. It involves multiple factors orchestrated by the estrogen and progesterone hormones in the reproductive organ.

Endometrial Cancer

EC is the most common gynecological malignancy affecting women in Western countries.[49] The risk factors include genetic disorders, obesity, diabetes mellitus, high levels of estrogen, and increasing age. The overall 5-year survival rate for EC is around 80%, mainly because patients are normally diagnosed at an early stage. Unfortunately, up to 20% of the EC patients relapse and eventually die due to the tumor spreading beyond the uterus when the diagnosis comes up at an advanced stage.[16] The most important prognostic factors comprise the tumor stage, histological grade, stage of disease, depth of myometrial invasion, lymphovascular space involvement (LVSI), and cervical involvement.[50]

Histology, molecular classification, and current treatments for endometrial carcinoma

EC is traditionally classified into two types based on their etiology and prognosis.[51] Type-I EC has a favorable prognosis as it is often diagnosed at an early stage. It has an endometrioid histological typology and often arises from endometrial hyperplasia in a setting of unopposed estrogen ambience in peri- and post-menopausal women. It commonly expresses high levels of ERα and PR.[52] Type-II tumors account for 10%–20% of ECs and often have a serous, papillary, or clear cell histology. They tend to be composed of markedly atypical cells that grow in papillary, glandular, or solid patterns.[52] Type-II tumors arise in the background of an atrophic post-menopausal endometrium independent of estrogen and may be preceded by endometrial intraepithelial carcinoma (EIC). Type-II tumors have a poor prognosis as they tend to spread from the site of origin early in the development of the disease.[52,53] In the last decade, molecular studies have generated promising results. An outstanding example is the molecular classification that divides EC into four categories: POLE-ultramutated (in association with a high histological grade and good prognosis), microsatellite instability (MSI), copy number low (CNL), and copy number high (CNH) (in association with p53 mutation and a worse prognosis).[54] The Cancer Genome Atlas Research Network (TCGA)[55] molecular classification for EC offers the opportunity to improve the current histological diagnosis and classification system, specify the prognostic information of each patient, adapt the indication of adjuvant treatments and assess the incorporation of therapies directed at certain types of targets or predict the response to them.[38,56,57]

The standard of care for the proper management of EC is surgical treatment. Adjuvant treatment consisting of radiotherapy or chemotherapy with platinum-based cytotoxic drugs, or in combination is indicated depending on factors that might impact on the recurrence and survival in EC.[58,59] The surgical extent is determined by the type of tumor (Type-I or Type-II), the histological grade and by the suspicion of extension of the disease determined by means of imaging tests.[60] Currently, in the initial stage of the pathology in Type-I tumors, the standard surgery consists of a total hysterectomy with double adnexectomy. The sentinel lymph node biopsy is normally considered for staging in patients with low and intermediate-risk disease to assess for the presence of pelvic nodal metastases as long as there is no extrauterine disease. In this group of patients, lymphadenectomy is not currently recommended since numerous studies have confirmed the validity of the sentinel node technique,[61] which has less post-surgical morbidity. In the case of patients with type-II tumors or type-I tumors with suspected infiltration $\geqslant 50\%$ of the myometrium, grade III or from stage II by imaging tests, total hysterectomy with double adnexectomy should be combined with a pelvic and para-aortic lymphadenectomy. In tumors with a serous, carcinosarcoma or undifferentiated histology, infracolic omentectomy is recommended. After the surgery, the requirement for chemotherapy or radiotherapy is discussed in a tumor multidisciplinary committee following clinical guidelines criteria.[58,59] The same occurs in cases of recurrence.

Immunotherapy using immune checkpoint blocked targeting, programmed death 1 (PD1) and programmed death ligand 1 (PDL1) is also emerging as an exciting new treatment for EC based on tumor characteristics and the molecular profile. Two drugs are currently approved by the EMA and/or FDA, pembrolizumab, and dostarlimab. Dostarlimab was granted accelerated approval for the treatment of patients with recurrent or advanced deficient mismatch repair (dMMR) EC that has progressed or following prior treatment with platinum-containing chemotherapy.[62] It is noted that the biomarkers MSI and PDL1 expression that often predict the response to immunotherapy are not frequently seen in the most aggressive EC forms.[63] These data confer less immunogenic profile than endometroid histology subtypes or early-stage serous ECs to advanced serous subtypes. However, a recent phase-II trial for the study of pembrolizumab in combination with lenvatinib (a multi-kinase inhibitor) has shown a 50% response rate in women with advanced serous endometrial

disease.[64] The progression-free survival (7.2 vs 3.8 months; HR 0.56) and the overall survival (OS: 18.3 vs 11.4 months; HR 0.62) were significantly improved with the combination of both versus pembrolizumab monotherapy.[65] Based on this study, pembrolizumab with lenvatinib was also approved in an accelerated manner by the FDA for patients with previously treated metastatic EC whose tumors were not MSI-H/dMMR.[66]

On the contrary, recent findings related to uterine cancer molecular drivers such as overexpression or amplification of the epidermal growth factor receptor 2 (HER2) in endometrial serous carcinoma has led the incorporation of several anti-HER2 therapies. That includes targeted therapeutic trastuzumab, which is associated with improved survival for women with advanced and recurrent HER2-positive disease when added to conventional chemotherapy.[65]

In the "ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma" that was updated in 2021,[58] information and bibliographic references are provided for the current management of EC.

Perineural invasion as a new route of metastasis in Endometrial Cancer as new route of metastasis in EC

Distant metastasis is still the leading cause of death in EC.[67] In addition to transcelomic invasion and lymphatic and hematogenic spread, the most common metastatic routes, PNI is the fourth route of tumor dissemination. PNI has been defined as the infiltration of the perineural sheath by tumor cells. It plays a crucial role in the progression of several carcinomas,[68] and it leads to a poor prognosis in head and neck squamous cell carcinoma, pancreatic cancer, and prostate cancer.[69,70] The biological interactions between nerves and cancer cells are vital in this process. However, the key drivers of PNI and its mechanisms are still largely unknown for the majority of cancers. In EC, Ti et al. have demonstrated, in in vitro neural invasion assays and transwell cocultures systems, the role of the dorsal root ganglion neurons to promote perineural metastasis of EC cells via AMPA receptor 2 (GluR2) as this effect was inhibited by both endogenous/exogenous knockdown of GluR2. Moreover, GluR2 was expressed in endometrial cell lines and also in endometrial tissue, suggesting that GluR2 could be a predictor of perineural metastasis in this type of cancer.[71] However, the prognostic value of PNI in EC is still unknown.

Sexual hormones influence in Endometrial Cancer

The lack of estrogen/progesterone balance normally dominated by estrogens can develop in EC formation.[72,73] Estrogen binds to nuclear ER resulting in the induction of growth factors like epidermal growth factor (EGF) and insulin-like growth factor-1 (IGF-1), the expression of EGF Receptor (EFGR), and the transcriptional factors c-fos and c-myc, as well as the activation of the PI3K/Akt pro-survival signaling pathway.[74,75] Genomic alterations are also observed, including transcriptional regulators that are linked to estrogens signaling.[76] Progesterone binds to nuclear PR to regulate varied signaling that leads to triggering transcriptional activity.[40] That transcriptional activity is modulated by a variety of miRNAs and epigenetic factors as has been widely demonstrated in animal models.[77] Estrogen signaling is known as one of the most important risks for EC, being ERα a key oncogene in EC.[74] Type-I endometrial tumors express high levels of ER and are hormonally driven, while Type-II tumors are less likely to express ER.[73]

As previously stated, neural regulation by estrogen and progesterone in the uterus oscillates over a woman's lifespan, depending mainly on the estrogen conditions. Particularly in EC, age-related neural plasticity does not suffer specific changes because the mean age on diagnosis of patients is 62 years old (menopausal state).[78] This point differs from the changes in hormone levels during the tumor progression in comparison with the lack of hormones after the surgical treatment, including the double adnexectomy discussed below (Figure 2(b))

An in-depth understanding of hormone influence in EC has led to the selective application of hormonal therapy in affected patients. Progestin therapies act by blocking estrogen-induced uterine growth and are indicated in young patients desiring uterine-sparing in the initial states of the disease.[79] Despite this, its application to avoid tumor recurrence after the surgery or in treating metastatic patients presents variable responses and more studies are needed to improve the treatment indication.

Neural influence in Endometrial Cancer

An influence of the innervation in tumor progression has been described in several gynecological cancers as well as in EC.[3,36] We hypothesize that similar to the pathophysiology of endometriosis,[14] there might be a redistribution of the endometrial layer nerve fibers in EC that creates an inflammatory tumor microenvironment (Figure 2). An overexpression of β-ADRs in tumor tissue relative to their matching to normal tissue has been reported in EC. This is especially true for β2-AR (IHC score normal vs cancer 0,0 vs 1,1), contrary to β1-AR and β3-AR (Table 1).[33] β3-AR, which stimulated lipolysis in human fat cells in physiologic conditions,[80] has been related to the metabolic syndrome. A genetic analysis has shown that the prevalence of an allele of the Trp64Arg polymorphism in this receptor gene might contribute to the susceptibility to EC among obese people.[81]

The influence of adrenergic signaling in EC was found indirectly through the evaluation of the stress response

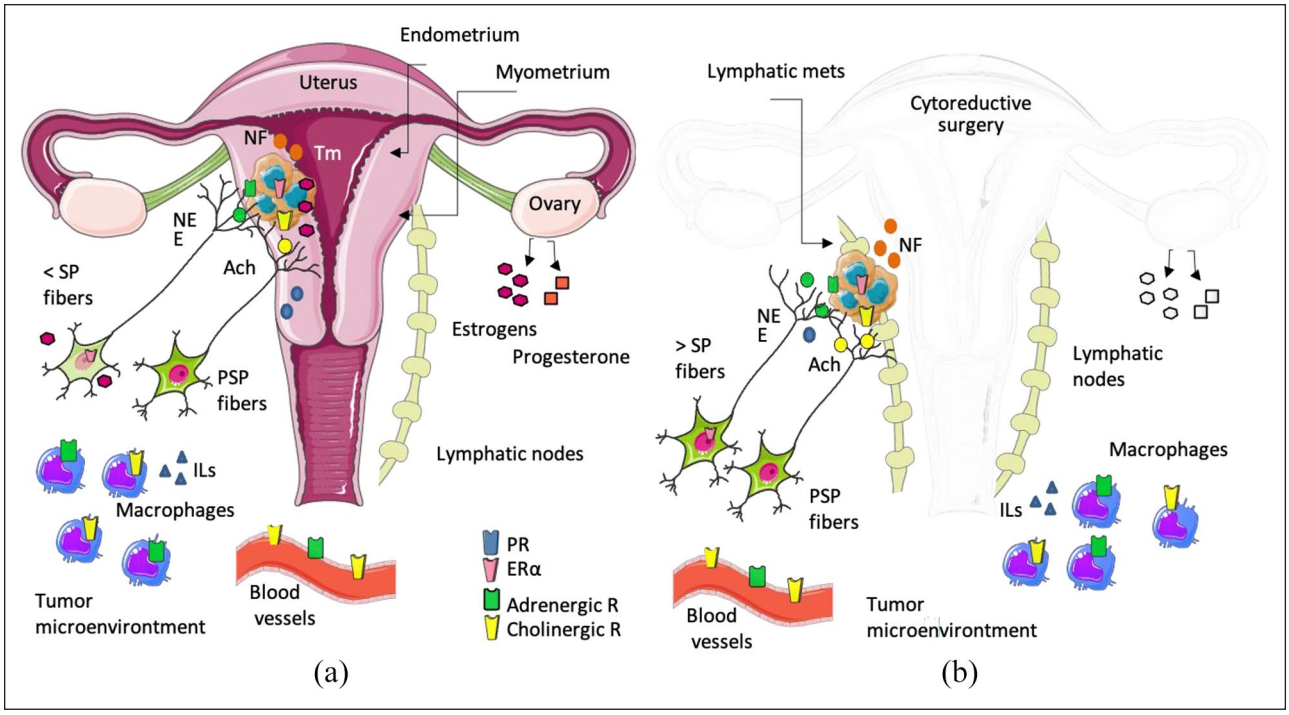

Figure 2. Nerve-cancer cell and sex hormone crosstalk: (a) Tumor progression. (b) Recurrence. Cancer cells can attract nerve fibers and stimulate nerve outgrowth by the paracrine secretion of neurotrophic factors (NF) in a process called neuroneogenesis. NFG contributes to the process and stimulates angiogenesis and inflammation. Tumor-associated macrophages also play an important role by secreting pro-inflamatory cytokines (IL-1, IL-6, IL-8, and TNF-α) that aid the tumor in circumventing antitumor responses. Conversely, nerve fibers secrete neurotransmitters (NE, E, ACh) that bind neuroreceptors in cancer and stromal cells (immune and endothelial cells) to stimulate tumor growth. Furthermore, estrogen has two effects, the induction of tumor growth by increasing estrogen signaling in cancer cells and the disruption of the sympathetic fibers, thereby giving prevalence to parasympathetic signaling (a). After surgical intervention, sex hormone levels are reduced and both sympathetic and parasympathetic signaling are active (b).

where adrenergic signaling is increased. The stress-induced release of catecholamine can activate β-ADRs in tumor cells and trigger increased expression of pro-angiogenic molecules like vascular endothelial growth factor (VEGF) in mouse model and cell lines.[82,83] It results in enhanced tumor vascularization, more aggressive growth and the spread of malignant cells (Figure 2(a)). Several studies have analyzed the mechanisms and their relationship with clinical results. In EC, serum levels of VEGF have been described as independent factors for poor prognosis.[84] Moreover, a recent study that experimented on cytokine array analysis in an adipose medium revealed that VEGF protein expression is upregulated in visceral adipose tissue in obese patients, which is correlated with increased tumor growth, vasculature promotion, and mTOR activity in in vivo xenograft models of EC.[85]

Cholinergic fibers, besides providing an important input to the uterus, are also detected in infiltrating endometrial tumors. A study that assayed the immunohistochemical expression of CHRM3 in 257 endometrial carcinoma patients has revealed that CHRM3 is highly expressed in advanced endometrial carcinoma and is closely correlated with the FIGO stage, vascular invasion, and lymphatic metastasis. This combination along with other clinicopathological risk factors is a stronger prognostic model and has significant clinical value in targeted therapy for endometrial carcinoma patients.[36]

Dopaminergic signaling is also active in ECs. Dopamine receptor type-2 (DRD2) is highly expressed in aggressive EC types (CNH, serous histology) and is associated with grade, stage, and worse OS and progression-free survival (PFS).[37] DRD2 antagonism with ONC201 potently inhibits cell proliferation in EC cell lines through the induction of apoptosis and increased cellular stress. ONC201 might be a novel targeting agent for EC neurotherapy, particularly in more aggressive EC types for which effective treatments are limited.[37,39] Another neural modulator described in EC is Substance P (SP). It is an undecapeptide that belongs to a family of tachykinins. SP is widely expressed in both the central and peripheral nervous systems and is also involved in endometrial carcinoma progression. SP preferentially binds to neurokinin-1 receptor (NK-1R) and induces the expression of vascular endothelial growth factor (VEGF) and promotes cancer cell proliferation and metastasis in endometrial adenocarcinoma.[86]

Neuronal elements are also necessary to create a tumor microenvironment. The innervation brought on by cancer cells is known to play an active role in tumor progression and invasion in different tumor types.[87] Cholinergic and adrenergic fibers release neurotransmitters that create a downstreaming signal to stimulate the corresponding receptors situated in immune cells (macrophages), stromal cells, and blood vessels. Multiple processes such as migration, invasion, and angiogenesis involve pro-inflammatory cytokines, chemokines, and neurotrophic factors to promote tumor growth. Conversely, the main tumor promotes raised innervation by mechanisms like axonogenesis based on the secretion of axon-guidance molecules and neurogenesis that stimulate the novo stem cells.[88] In the same tumor microenvironment, estrogen and progesterone hormones maintain paracrine connections with nerves terminals. Evidence indicates that changes in circulating estrogen mediated through ERα are determinant of variations in uterine sympathetic innervation[89] (Figure 2).

Compared to other solid tumors, there is room for unveiling the neural influence in EC and the mechanisms that neurotransmitters and neuroreceptors apply to activate oncogenic pathways. Autonomic nervous system contribution has been widely studied in breast cancer including the impact of stress on tumor progression.[90,91] Breast cancer is a heterogeneous disease mainly characterized by the status of HER2, the estrogen receptor and the progesterone receptor of the primary tumor. The well-known biological effects of stress on breast tumor progression may be because of its high incidence, as it is the most common cancer in women, together with the extended experience in experimental models of this tumor.[92] However, the role of the different adrenergic receptors, especially β2AR, expressed in tumors and different stroma cells is still under research. Although a study demonstrated that there was a higher incidence of EC in patients with both estrogen receptor–positive or –negative breast cancer than in the general population,[93] the influence of estrogen in the crosstalk between nerves and breast tumors has not yet been studied. Similar to EC, neural plasticity may be implicated. It would be an interesting area of study.

Neural therapy in cancer and perspectives for Endometrial Cancer

Anti-neurogenic therapies have been applied extensively for the treatment of pain, cardiovascular disorders, mental disorders, and anxiety. However, they also have been redirected to oncology treatments under the so-called "drug repurposing" policy. It implies testing for new indications of existing drugs using information on pharmacokinetics, safety, and the manufacturing of the medication. This would make it a very cost-efficient treatment strategy.[94]

Targeting neurotransmitters and their receptors in cancer

Among the neural targets, the neurotransmitters are highly investigated molecules thanks to their capacity to enable communication between neurons. The use of repurposed drugs is supported by the results obtained in clinical trials with patients taking beta-adrenergic antagonists for the treatment of cardiovascular disorders and anxiety. They presented with increased OS in prostate, breast, and ovarian cancers.[95–97]

Beta-adrenergic antagonists may mediate the inhibition of the stimulatory effect of catecholamines released by nerves in the tumor microenvironment through a mechanism that continues being investigated. Other evidence to support the use of the anti-neurogenic therapy is based on data on stress-induced cancer development related to surgical stress, psychological stress, and depression.[98] The higher circulation levels of E and NE that favor tumor activation can be prevented with the use of β-blockers. This mechanism has been experimented with in mouse models of pancreatic ductal adenocarcinoma.[99] Furthermore, common therapies for stress and anxiety disorders like benzodiazepines and SSRIs also inhibit the proliferation and migration of cancer cells in vitro.[100]

Currently, more than 20 clinical trials[101] are ongoing to evaluate the therapeutic efficacy (alone or in combination) of antagonists or agonists of adrenergic receptors. Although clinical responses are pending assessment, mechanisms such as the decreased induction of neurites, a decline in nerve-cancer interaction and less neurotrophin secretion have been proposed for tumor innervation inhibition brought on by these treatments.[3] The most used is propranolol, a non-selective beta-adrenergic antagonist. It has been tested in the treatment of several gastrointestinal cancers, prostate cancer, hepatocarcinoma, recurrent breast cancer, cutaneous melanoma, renal cell carcinoma and hemangioma.[102] In addition, metoprofol and esmolol, selective β1-AR antagonists, have been accepted for the treatment of solid tumors, hematological malignancies and intracranial tumors.[103] Relative to uterine cancers, a recent study that presented experimental data proved that propranolol can block the cGMP-PKG signaling pathway in cervical cancer cells.[104]

Differently, the activation of dopaminergic signaling, and not the inhibition of adrenergic signaling, has an antitumor effect. It has also been associated with apoptosis induction in breast cancer cells. Therefore, the use of D2-agonists in dopamine receptor expressing tumors seems to be a promising tool as a complementary therapy in breast cancer.[105] There are ongoing clinical trials to evaluate cabergoline (D2 and D3 dopamine receptors) in metastatic and recurrent breast cancer.[101] Regarding cholinergic receptors, a muscarinic antagonist currently used in the treatment of the overactive bladder (e.g. darifenacin)

seems to arrest tumor progression in small-cell lung carcinoma.[106] However, the potential therapeutic effects of cholinergic antagonists are still under investigation.[107]

Targeting neurotrophins and their receptors in cancer

Nerve growth factor (NGF) plays a significant role in pain generation.[94] Many strategies like blocking with antibodies, small pharmacologic inhibitors, and peptides have been designed to antagonize NGF and its receptors TrkA and p75NTR.[108] Interestingly, a humanized monoclonal antibody (tanezumab) that has been validated in mouse models is already in clinical trials for its analgesic activity in chronic rheumatoid arthritis and back pain. In it, anti-NGF antibodies have been shown to decrease the pain caused by bone metastases from prostate cancer and to attenuate bone destruction.[109] Beyond this role in the pain process, Pro-NGF and NGF, through their TrkA and p75NTR receptors, stimulate tumor cell growth and invasion in breast[110] and prostate cancer cells.[111] Furthermore, involvement has been seen in the proliferation in the stem cell compartment.[112] Other neurotrophin expressions like the brain-derived neurotrophic growth factor and its receptor TrkB strongly contribute to proliferation and dissemination in gastric tumor cells.[113] Altogether, the identification of neurotrophic factors like inductors of tumor cell growth, the dissemination of many cancer cells as well as the drivers of nerve infiltration in tumors also support the use of these molecules as a new neurotherapeutic approach.

Anti-neurogenic treatment perspectives in Endometrial Cancer

Many patients undergoing surgery achieve clinical remission, but advanced-stage cancer is prone to recurrence.[67] A deeper understanding of nerve dependence can contribute to the use of the targeted anti-neurogenic therapy presented as a novel tool in the management of EC adjuvant to standard treatments.

Anti-neurogenic therapy targeting sympathetic nerves using adrenergic antagonists has been evaluated as a novel strategy to control tumor growth in other cancers. However, in EC, contrary to others, the status of sympathetic innervation is variable and highly influenced by estrogen and progesterone hormones. Until now, no prospective studies have evaluated possible anti-neurogenic therapies specifically for EC. The linkage between EC survival and β-blockers was only evaluated in a UK population-based study without any significant results.[114] The success of a potential anti-adrenergic therapy may depend on the status of residual sympathetic innervation and the levels of circulating estrogen and progesterone. The ovaries are the main productors of estrogen, and the bilateral oophorectomy undergo in surgery influences the level of this hormone. Low levels of estrogen given after surgical intervention might enhance sympathetic signaling that leads to a protumorigenic response. It is known that the sympathetic nerves are a determinant factor in endometrial tumor progression and recurrence (Figure 2(b)). Based on this hypothesis, it would be interesting to investigate the relationship between sympathetic innervation and sex hormones in the early and late stages of EC to provide new information related to recurrences as well as new treatments for EC patients.

Conclusion

Patients affected by EC are diagnosed in the early stages and have high rates of survival. However, these rates are reduced dramatically if regional or distant spread is involved. Nerves have been reported to play an active role in tumor progression and invasion, and they are associated with aggressiveness and a poor prognosis in several cancers. The status of estrogen and progesterone levels is one of the major risk factors in developing EC and might influences nerve innervations and subsequently EC progression. Further studies should be done to evaluate the relationship between hormonal status, nerve plasticity, and EC. This could lead to uncovering interesting information for the diagnosis, prognosis, and management of EC. Moreover, those studies might bring about new therapeutic options (anti-neurogenic), alone or in combination with standard therapies to improve the health and quality-of-life of women.

Author contribution(s)

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Rocio Luna: Data curation; Formal analysis; Visualization; Writing—original draft.
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Ethics committee

The Ethics Committee of the *Hospital de la Santa Creu i Sant Pau* waived the need for ethics approval of the present manuscript for its main characteristics as it is a non-interventional study where no medications or patients are involved.

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