REVIEW ARTICLE

Modulatory effect of innervation on endometrial cancer

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Abstract

Research on cancer neurobiology has shown that the nervous system plays an important role in the initiation and progression of many types of cancer in humans, including breast, gastric, pancreatic, colorectal, and prostate cancers. Although endometrial cancer is not in the center of cancer neurobiology research, accumulating data indicate that sympathetic, parasympathetic, and sensory nerves innervating uterus modulate the initiation, progression, and metastasis of endometrial cancer. However, compared to other types of cancer, data related to the role of nerves in endometrial cancer are sparse and inconsistent. Therefore, the aim of this review is to analyze available data related to physiological effects of nerves innervating uterus and endometrium and the modulatory effect of these nerves on endometrial cancer and to depict further research directions.

Introduction

Recently, combined neuroscientific and oncological research uncovers mechanisms and pathways mediating the modulatory effect of the nervous system on cancer initiation and progression (Mravec, 2022). Importantly, available data indicate that similar to other human cancers, the nervous system plays a role also in endometrial cancer, as well.

In general, the modulatory effect of the nervous system on cancer is mediated via nervous and humoral pathways that affect both tumor macro-, and microenvironment (Ondicova & Mravec, 2010). At the level of the tumor microenvironment, the nerves innervating the cancer play an important role. Whether these nerves stimulate cancer initiation and progression depends on the nerve phenotype (sympathetic, parasympathetic, or sensory), their density, and the type of tissue or organ of cancer origin (Ali *et al.* 2022; Baraldi *et al.* 2022).

The uterus is innervated by sympathetic, parasympathetic, and sensory nerves which play an important role in modulating its cellular and tissue homeostasis. In general, these nerves modulate in tissues processes related to cell proliferation, angiogenesis, blood flow, and inflammation. Importantly, from the perspective of endometrial cancer, nerves play significant role in regeneration and repair (Boilly *et al.* 2017), processes that are linked to cyclic physiological changes in the endometrium. Therefore, it can be assumed, that alter-

ations in the modulatory effects of nerves innervating the uterus (Fig. 1) may initiate or potentiate cellular and tissue abnormalities participating on development and progression of endometrial cancer and the development of metastasis.

The aim of this review is to analyze the available data related to the role of nerves in the initiation and progression of endometrial cancer and to outline possible directions for further research.

Endometrial cancer

Endometrial tumors are the most common type of gynecological malignancy in women (Corr *et al.* 2022; Siegel *et al.* 2022). Based on etiology and prognosis the endometrial cancer is divided into two types of tumors (Bokhman, 1983). Type I of endometrial tumors have favorable prognosis, endometrioid histology, high expression levels of estrogen receptor type α and prolactin receptor and often arises from endometrial hyperplasia. Type II of endometrial tumors have a poor prognosis with tend to metastasis, serous, papillary or clear cell histology and arise from an atrophic post-menopausal endometrium and endometrial intraepithelial carcinoma (Di Cristofano & Ellenson, 2007; Espanol *et al.* 2022). According to the newer histological classification the endometrial cancer is divided into several subgroups – endometrioid, serous, clear cell, mixed cell adenocarcinomas, and other relatively rare types including mucinous adenocarcinoma, neuroendocrine tumors (small cell, large cell carcinoma, carcinoid tumor), dedifferentiated carcinoma and undifferentiated carcinoma (Yen *et al.* 2020). Molecular based classification divides endometrial cancer into four groups – POLE-ultramutated (characterized by somatic mutations in the polymerase epsilon DNA polymerase – POLE exonuclease domain), microsatellite instability (with deficiencies in the DNA mismatch repair system), copy number low and copy number high (both based on copy number alterations) (Yen *et al.* 2020; Corr *et al.* 2022).

Innervation: new hallmark of cancer

Presence of nerves in cancer tissue and its role cancer initiation and progression is object of research for more than century. Data accumulated in the last two decades have clearly shown that nerves play an important role in cancer and therefore it is suggested that innervation represents a new hallmark of cancer (Vermeer, 2019; Restaino & Vermeer, 2022).

Depending on tissue of origin, cancer tissues might be innervated by sympathetic, parasympathetic, and sensory nerves (March *et al.* 2020; Prazeres *et al.* 2020; Restaino & Vermeer, 2022). In tumor microenvironment, sympathetic nerves release neurotransmitters such as norepinephrine and neuropeptide Y, parasympathetic nerves release acetylcholine, whereas sensory nerves release substance P and calcitonin-gene related peptide. These neurotransmitters and neuromodulators binding to their corresponding receptors localized on cancer cells and non-cancerous cells in tumor microenvironment (e.g., immune cells, fibroblasts) and activate the relevant signaling pathways that directly affect processes of tumor growth and metastasis (Entschladen *et al.* 2006; Faulkner *et al.* 2019).

Nerves localized in cancer tissue have several origins: a) nerves that were present in tissue of cancer origin; b) new nerve fibers that grow into cancer tissue from nerves innervating tissue surrounding cancer (neoaxogenesis); c) nerve fibers of new neurons migrating from distant parts of the central nervous system or peripheral nervous system to the tumor tissue or its proximity (Mauffrey *et al.* 2019; Amit *et al.* 2020).

In addition to the effect of neurotransmitters and neuromodulators released from nerves into tumor microenvironment, nerves might play also "mechanical" role in cancer progression. Namely, nerves innervating cancer may represent bridge enabling cancer cells move via perineural spaces from cancer tissue to surrounding tissue. This process, named perineural invasion (PNI), is based on mutual cooperation of Schwann cells, tumor cells and axons. On the one hand, it enables spread of cancer cells, on the other hand, it also stimulates neoaxogenesis in tumors (Deborde *et al.* 2016; Yoneda *et al.* 2021).

Innervation of uterus

The autonomic nerve fibers in uterus are more abundant in the cervix and endometrial junction. Moderate nerve density is in the circular and longitudinal smooth muscle of the myometrium and abundant around the blood vessels (Zoubina *et al.* 1998).

Nerve fibers innervating the uterus show a remarkable range of physiological plasticity. For example, after puberty, there is a significant and irreversible decrease in the density of sympathetic nerves. These nerves also undergo cyclical phases of degeneration and regeneration during the estrous cycle. An experimental study performed on uterine samples obtained from normal cycling women showed, that in early proliferative endometrium are only a few small nerve fibers, while in lower half of *lamina functionalis* from mid-secretary phase are more nerve fibers. Late-secretary *lamina functionalis* showed less nerve fibers in the upper-half than the lower-half of *lamina functionalis* (Tomita, 2014). In addition, sympathetic nerves degeneration occurs during pregnancy, while they regenerate after delivery, as demonstrated also by the study in virgin, pregnant, and lactating rats, in which transsynaptic viral labelling of central nervous system structures from the uterine horn was performed (Wiesel *et al.* 2004). It is assumed that the plasticity of the uterine nerves is a consequence of the action of sex hormones, which affect the ability of the uterine tissue to maintain innervation through

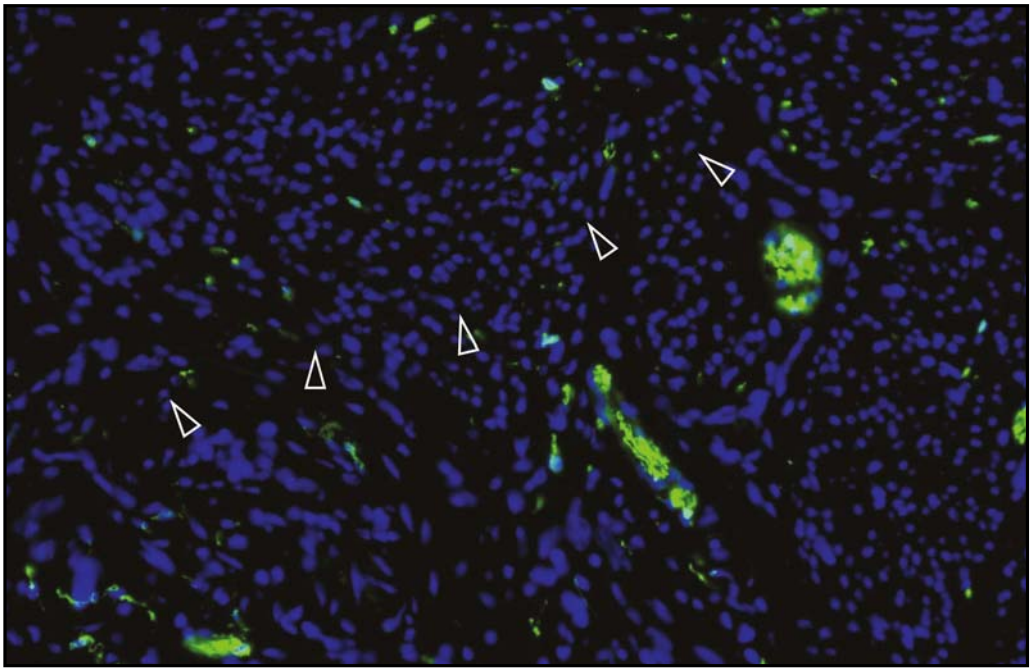

Fig. 1. Endometrioid carcinoma infiltrating the uterine wall. Note dispersed small nerve filaments in the tumor (delineated by arrowheads) and large and smaller nerves in the uterine muscle. Nerves are detected with anti-S100 antibody showing yellow fluorescence, nuclei are blue. Indirect immunofluorescence, 100x.

changes in the neuritogenetic properties of this tissue (Brauer, 2008; Espanol *et al.* 2022). In support of this, sympathetic hyperinnervation of uterus was reported in mice with a null mutation of the estrogen receptor α (Zoubina & Smith, 2001).

Sympathetic innervation and endometrial cancer

Sympathetic innervation of uterus is provided by inferior hypogastric plexus, which receives postganglionic sympathetic nerve fibers from the left and right inferior hypogastric nerves, which are the branches of the superior hypogastric plexus. The cell bodies of sympathetic preganglionic neurons are localized in intermediolateral cell column of the Th12-L2 spinal cord. These neurons project their preganglionic nerve fibers through the sympathetic chain into the inferior mesenteric ganglion where they create synapses on sympathetic postganglionic neurons (Paraskevas *et al.* 2008; Espanol *et al.* 2022). Under physiological conditions, sympathetic nerves regulate uterine contractions during gravidity through α_1-adrenergic receptors, and relaxation of not pregnant uterus through β_2-adrenergic receptors (Sato *et al.* 1996).

In general, norepinephrine released from sympathetic nerve endings and binding to β-adrenergic receptors expressed by cancer cell, stimulates cancer cell proliferation and invasion (Cole & Sood, 2012; Magnon *et al.* 2013; Restaino & Vermeer, 2022). Mechanistic studies have shown that activation of β-adrenergic signaling in tumor cells can increase expression of vascular endothelial growth factor (VEGF) and therefore enhance tumor vascularization, followed by more aggressive growth and the spread of malignant cells (Armaiz-Pena *et al.* 2013; Zahalka *et al.* 2017; Yap *et al.* 2018). Compared to the normal tissue, there was documented overexpression of β-adrenergic receptors in endometrial cancer, especially of β_2-adrenergic receptors subtype (Rains *et al.* 2017). Interestingly, administration of β-adrenergic receptors antagonists (β-blockers) to patients with endometrial cancer led to reduction in disease-free survival and overall survival (Yap *et al.* 2018). For example, in relation to uterine cancer, there was revealed that β-adrenergic receptor antagonist, propranolol, suppresses cGMP/PKG signaling pathway and caused apoptosis of human cervical cancer cells (Gong *et al.* 2019). The role of β-adrenergic signaling in patients affected by gynecological malignancies was suggested by an experimental study focused on influence of β-adrenergic receptors antagonists, propranolol and bupranolol, on contractile activity of the nonpregnant human uterus. The gynecological malignancies considerably altered the contractile activity of the nonpregnant human uterus in response to β-adrenergic receptors antagonists (Modzelewska *et al.* 2021). The experimental study performed on human endometrial cancer cell line showed that administration of anticancer acting substance, platycodine D, lead to markedly decreased proliferation, invasion and migration of endometrial cancer cells, and reduced activation of the PI3K/Akt signaling pathway in endometrial cancer cells. Additionally, α_{2A}-adrenergic receptor expression was elevated in endometrial cancer cells, which is normally low in endometrial tumors (Ni *et al.* 2023).

Several studies pointing on the association of β_3-adrenergic receptor gene mutation (replacement of tryptophan at position 64 by arginine – Trp64Arg) with obesity and *diabetes mellitus*, which are the predisposing factors for endometrial cancer (Iwamoto *et al.*

2003). In this regard, there was revealed that Trp64Arg allele prevalence in the gene of β3-adrenergic receptor may contribute to the susceptibility to endometrial cancer among obese people (Babol, 2004). In addition to this, VEGF is overexpressed in visceral adipose tissue of obese patients, which is positively correlated with the increased tumor growth and neoangiogenesis (Sahoo *et al.* 2018).

Parasympathetic innervation and endometrial cancer

The cell bodies of preganglionic parasympathetic neurons are localized in the intermediolateral cell column of the S2-S4 spinal cord. These neurons project their nerve fibers via ventral roots of the spinal cord, travel via pelvic splanchnic nerves and create synapses in parasympathetic ganglia localized in the wall of uterus (Paraskevas *et al.* 2008; Espanol *et al.* 2022). Under physiological conditions, parasympathetic nerves mediate uterine contraction through muscarinic receptors type 2 and 3 (M2, M3) and relaxation of the uterine blood vessels (Sato *et al.* 1996).

In general, parasympathetic nerves affect only some cancer types, especially cancers of the gastrointestinal tract. This restricted effect appears to reflect their functional specialization, in contrast to more globally acting sympathetic nerves (Faulkner *et al.* 2019; March *et al.* 2020).

Immunohistochemical analysis of endometrial carcinoma specimens revealed correlation between M3 expression and vascular invasion and lymphatic node metastasis (Wang *et al.* 2015). However, the role of parasympathetic nerves and potential therapeutic effects of cholinergic agonists and antagonists in endometrial cancer needs further investigation.

Sensory innervation and endometrial cancer

Visceral sensory nerves innervating uterus mediate mechanoreception, thermoreception, and nociception. The cell bodies of primary afferent neurons are located in the dorsal root ganglion (Keskinov *et al.* 2016). In addition, the uterine tissue is also innervated by vagal afferent neurons, the bodies of which are located in nodose ganglia (Collins *et al.* 1999). Sensory nerves innervating uterus reach also the endometrium.

Besides transmission of sensory information into central nervous system, sensory neurons also modulate processes in innervated tissues. This effect is mediated via axon reflex (Holzer, 1988).

Several findings indicate that sensory nerves, similar to autonomic nerves, may influence cancer (Keskinov *et al.* 2016; Saloman *et al.* 2016; Prazeres *et al.* 2020). Experimental studies showed that substance P, through neurokinine-1 receptor (NK-1R), and calcitonin-gene related peptide, through RAMP1/CALCRL complex, stimulate cancer cell proliferation, angiogenesis and metastasis in several cancer types (Kelley *et al.* 1994; Nagakawa *et al.* 1998; Mehboob *et al.* 2015).

Regarding to endometrial cancer it was shown that substance P through NK-1R induces VEGF expression and promotes cancer cell proliferation and metastasis (Ma *et al.* 2016). Interestingly, compared to the control group, in patients with endometrial cancer were detected higher levels of serum substance P and increased expression of NK-1R in cancer tissue. In addition, positive correlation between NK-1R expression and lymph node metastasis was demonstrated. These findings indicate that substance P/NK-1R affect tumor growth and development in endometrial cancer (Gharaee *et al.* 2018).

Sensory nerves might participate on development of endometrial cancer metastasis also via the process of perineural invasion. In support of this, using *in vitro* neural invasion assays and transwell cocultures systems, it was showed, that neurons of dorsal root ganglia can promote perineural invasion of endometrial cancer cells through AMPA ionotropic glutamate receptor-mediated mechanism (Ni *et al.* 2020).

Future directions

In many cancers, sympathetic nerves potentiate their progression and development of metastasis. This effect is confirmed by studies showing that application of β-blockers, drugs that block stimulatory effect of main sympathetic neurotransmitter norepinephrine on tumor micro- and macroenvironment reduce proliferation of cancer cells *in vitro* and *in vivo*. However, it is necessary to note that the inhibitory effect of β-blockers results mainly from the blockade of β_2 subtype of adrenergic receptors. Interestingly, a retrospective clinical study indicated no significant association of the β-blockers treatment with survival of women with endometrial cancer (Sanni *et al.* 2017). However, in this study, there were no separately evaluated effects of selective and nonselective β-blockers and therefore it is possible that potential survival-prolonging effect of blockade of β_2-adrenergic receptors was masked by the infectivity of selective β_1-blockers (similar masked effect was observed also in a retrospective study in women with breast cancer (Mravec, 2021)). Therefore, more appropriately designed clinical studies needs to be performed to determine whether sympathetic nerves do potentiate endometrial cancer. In addition, *in vitro* studies exposing endometrial cancer cells lines to adrenergic and cholinergic receptors agonist and antagonist might elucidate the role of autonomic nerves in endometrial cancer.

Conclusion

From the point of view of neurobiology, endometrial cancer shows certain peculiarity. First, compared to other somatic tissues, the endometrium exhibits

marked neuroplasticity, indicating that nerves may play an important role not only in physiological processes but also during malignant transformation and progression of endometrial cancer. Second, compared to other types of cancer, unfortunately there are limited data related to the role of nerves in endometrial cancer. These limited data indicate that sympathetic, parasympathetic, and sensory nerves may play a role in endometrial cancer progression and metastasis. However, these data are inconsistent and more detailed research will be needed. Further research could elucidate the potential role of nerves in endometrial cancer initiation and progression in more detail and lead to the introduction of new therapeutic approaches for patients with this disease.

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