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Editorial

Neuron-Tumor Interaction in Prostate Cancer: Implications and Future Perspective

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HIGHLIGHTS

- Perineural invasion is a process that leads to the destruction of the perineurium caused by the invasion of tumor cells, followed by neuronal repair and inflammation in the perineural niche, promoting survival and encouraging further regional metastasis.
- Prostate tumor development is promoted by the impact of β2- and β3-adrenergic receptors. In contrast, migration and metastasis of prostate tumor cells are linked to Chrm1 cholinergic receptors.
- PD-L1+ tumor-associated nerves in the tumor microenvironment can significantly attenuate the anti-tumor immune responses launched by CD8+ tumor-associated lymphocytes.

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ABSTRACT

Neural elements are essential components of the tumor microenvironment (TME) in various tumors, including prostate cancer. Based on their structure and function, prostate neurons originate from different sources, such as the hypogastric and pelvic nerves. Neuronal factors of TME can lead to tumor development and metastasis based on their specific receptors. Tumor cells can follow a specific path of metastasis through perineural invasion (PNI). However, the mechanisms of PNI as an essential factor associated with poor prognosis have not yet been entirely elucidated. Moreover, the interaction between neural components of TME and the immune system plays a crucial role in tumor progression. Although targeting the neuron-tumor interplay has not yet reached the clinical stages, further studies may pave the way for new therapeutic strategies.

Keywords: Prostate Cancer; Tumor Microenvironment; Perineural Invasion; Neuron-Tumor Interaction; Tumor-Associated Nerves

Editorial: The tumor microenvironment (TME) comprises different types of stromal cells, including cancer-associated fibroblasts, adipocytes, myogenic cells, mesenchymal stem cells, immune cells, endothelial cells, and neurons. The TME is crucial in providing a favorable environment for tumor growth, survival, and dissemination through

complex signaling pathways (1-3).

Prostate neural components can be originated from various sources. The prostate gland receives sympathetic neurons from the hypogastric nerve and parasympathetic neurons from the pelvic nerve (4). The prostate epithelium is innervated with cholinergic fibers, while noradrenergic fibers are predominant in the peripheral stromal tissue of the prostate (5, 6). Moreover, neuronal progenitors can migrate from the brain subventricular zone to the prostate tumor area through the bloodstream and differentiate into new adrenergic neurons (7).

Perineural invasion (PNI) is a process in which prostate tumor cells invade nerve endings by damaging the perineurium, leading to the development of a distinct microenvironment known as the perineural niche (8). This niche comprises neurons, endothelial cells, immune cells, neurotransmitters, chemoattractants, and extracellular matrix (9). Upon invasion into perineurium and onset of inflammation and wound-healing processes, injured neurons and other stromal cells promote tumor cell survival, proliferation, and infiltration (10). The occurrence of PNI is considered a factor correlated with low survival rate and poor prognosis in several tumors, including prostate cancer (9).

Emerging evidence suggests that neural cells in TME can contribute to various pathways involved in the development and progression of prostate cancer. Previous studies have shown that prostate cancer growth is linked to the influence of adrenergic fibers from the sympathetic system. In contrast, the migration and metastasis of prostate cancer are facilitated by the impact of cholinergic fibers from the parasympathetic nervous system through the Chrm1 receptor on tumor cells (11). A study conducted by Magnon et al. demonstrated that the double knockout of β2- and β3-adrenergic receptors in mice models of prostate cancer significantly reduces tumor development (11). Additionally, axonogenesis can be stimulated along with tumor dissemination into surrounding tissues (11, 12). According to Coarfa et al., mice subjected to bilateral denervation of the Major Pelvic Ganglia exhibited a decrease in both tumor size and incidence (13). Furthermore, beta-blockers have been shown to decrease the mortality rate of prostate cancer patients by inhibiting the beta receptors on the adrenergic fibers of the sympathetic nervous system, reducing prostate cancer growth (14).

The crosstalk between neural and immune system components can have a remarkable impact on the development and progression of prostate cancer. In particular, the neurons of TME can interact with the immune system and attenuate the anti-tumor response. According to the study by Ru-Jun Mo et al., PD-L1 was expressed in prostate cancer patients' tumor-associated nerves (TANs). These PDL1+ TANs were negatively associated with the amount of CD8+ tumor-associated lymphocytes, and their high density was positively associated with biochemical recurrence and poor prognosis (15).

Conclusion

Although targeting the TME's neural components has not yet been thoroughly tested in the clinical phase, promising preclinical and preliminary clinical results encourage combining these strategies with standard treatments such as chemotherapy or radiotherapy. By focusing on the signaling pathways involved in neuron-tumor interactions or using therapeutic agents to target neural receptors, new avenues can be opened to reshape the future of prostate cancer treatment.

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Conflict of interest

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Data availability

None.

Abbreviations

PNI	Perineural Invasion
TANs	Tumor-Associated Nerves
TME	Tumor Microenvironment

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