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Вохидова Зебо Толибовна
Стажер-ассистент Кафедра оперативная хирургия и топографической анатомия Самаркандский государственный медицинский университет

НЕЙРОПАТИЯ, СВЯЗАННАЯ С РАКОМ И ЛЕЧЕНИЕМ, ПРИ РАКЕ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

Резюме: Рак поджелудочной железы характеризуется глубоким взаимодействием с нервной системой как на периферическом, так и на центральном уровнях. На локальном уровне рост опухоли вызывает аксоногенез, ремоделирование нервных волокон, периневральную инвазию и периневральный неврит. Системно рак поджелудочной железы поражает центральную нервную систему посредством внутриопухолевых и связанных с кахексией факторов, способствуя центральным нейропатическим изменениям. Эти нейрональные изменения играют решающую роль в инициации опухоли, ее прогрессировании и тяжести симптомов. Кроме того, химиотерапевтически индуцированная нейропатия является частым осложнением, приводящим к повреждению периферических нервов и когнитивным нарушениям.

Ключевые слова: Рак поджелудочной железы, периферическая нервная система, центральная нервная система, аксоногенез, ремоделирование нервных волокон, периневральная инвазия, периневральный неврит, внутриопухолевые факторы, связанные с кахексией.

Voxidova Zebo Tolibovna
Stajor-assistant, candidate of medical sciences
Department of Operative Surgery and Topographic Anatomy Samarkand State Medical University

CANCER- AND TREATMENT-RELATED NEUROPATHY IN PANCREATIC CANCER

Resume: Pancreatic cancer is characterized by profound interactions with the nervous system at both peripheral and central levels. Locally, tumor growth induces axonogenesis, neural remodeling, perineural invasion, and perineural neuritis. Systemically, pancreatic cancer affects the central nervous system through

tumor-intrinsic and cachexia-associated factors, contributing to central neuropathic alterations. These neural changes play critical roles in tumor initiation, progression, and symptom burden. In addition, chemotherapy-induced neuropathy is a frequent complication, leading to peripheral nerve injury and cognitive impairment.

Keywords: Pancreatic cancer, peripheral nervous system, central nervous system, axonogenesis, neural remodeling, perineural invasion, perineural neuritis, tumor-intrinsic, cachexia-assosiated factors.

Abstract: Pancreatic cancer is associated with profound changes in the nervous system, including enhanced axonogenesis, neural remodeling, perineural invasion, and perineural inflammation. In addition to local neural alterations, pancreatic cancer can affect the central nervous system through tumor-intrinsic mechanisms and systemic factors, particularly those related to cancer cachexia. These peripheral and central neuropathic alterations play important roles in tumor initiation and progression. Furthermore, chemotherapy-induced neuropathy is frequently observed in pancreatic cancer, leading to peripheral nerve injury and cognitive impairment. Therapeutic strategies aimed at disrupting the bidirectional interactions between pancreatic cancer and the nervous system, at both peripheral and central levels, may offer novel opportunities to inhibit tumor progression, alleviate pain, and improve patient quality of life.

Introduction

Pancreatic cancer is among the deadliest malignancies, largely due to its late clinical presentation and highly aggressive biological behavior. Its development is driven by a complex interplay of genetic and molecular alterations, most notably activating mutations in the *KRAS* oncogene, which are present in more than 90% of cases.[1,2,4] Tumorigenesis follows a multistep progression model in which low-grade precursor lesions gradually accumulate additional genetic abnormalities, including inactivation of key tumor suppressor genes such as *TP53*, *SMAD4*, and *CDKN2A*, ultimately giving rise to high-grade lesions and invasive pancreatic cancer.[3;10]]

Under normal physiological conditions, the pancreas is extensively innervated by both intrinsic and extrinsic neural components. Similar to other gastrointestinal organs, its extrinsic innervation consists of sympathetic, parasympathetic (primarily via the vagus nerve), and sensory fibers. Sympathetic preganglionic neurons originate in the intermediolateral cell column of the thoracic spinal cord (T5–T9 segments), while parasympathetic and sensory pathways further contribute to the regulation of pancreatic secretion, blood flow, and tissue homeostasis.[5;6]

In pancreatic cancer, this tightly regulated neural architecture undergoes profound pathological remodeling. Human pancreatic tumors are characterized by marked intrapancreatic neural alterations, including increased nerve size (neural hypertrophy) and nerve number (enhanced neural density). Emerging evidence highlights dynamic, bidirectional interactions between tumor cells and nerves, driven by processes such as axonogenesis, neurogenesis, and neural remodeling, which collectively support tumor growth and progression.

A prominent feature of pancreatic cancer is perineural invasion, a process in which cancer cells penetrate the perineurium and establish close contact with axons and Schwann cells within the endoneurium. Perineural invasion is strongly associated with severe abdominal neuropathic pain, increased local recurrence, and reduced survival following surgical resection. Moreover, invasion of extrapancreatic nerve plexuses facilitates both local extension and distant dissemination of tumor cells, underscoring the clinical importance of neural involvement in disease progression.

In addition to structural invasion, pancreatic cancer–associated nerves frequently exhibit inflammatory changes known as perineural neuritis. Hypertrophic nerves are often infiltrated by immune cells, including $CD8^+$ cytotoxic T lymphocytes, macrophages, and mast cells. Nerve fibers are also commonly observed within tertiary lymphoid structures in pancreatic tumors, which are enriched in $CD20^+$ B cells, suggesting a complex neuroimmune microenvironment that may influence tumor behavior and patient symptoms.[8,9]

Beyond tumor-induced neural remodeling, chemotherapy represents another major source of neural injury in pancreatic cancer. Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating adverse effect of standard treatment regimens, including those used in neoadjuvant and adjuvant settings. CIPN manifests as peripheral nerve dysfunction and, in some cases, cognitive impairment, significantly affecting treatment tolerance and quality of life.

Importantly, the impact of pancreatic cancer on the nervous system extends beyond the periphery to involve the central nervous system (CNS). Neural invasion and systemic tumor-derived factors can induce CNS remodeling, contributing to cancer-associated cachexia through activation of astrocytes and central neural circuits. Schwann cells, which play a key role in peripheral nerve repair, also modulate spinal astroglial and microglial activity, linking peripheral nerve injury to central neuroinflammatory responses. Tumor-derived signals, such as hypoxia and interleukin-6, further activate Schwann cells and amplify these neurobiological effects.

Accumulating evidence demonstrates that pancreatic cancer is highly dependent on neural inputs for its initiation and progression. Sympathetic, parasympathetic, and sensory nerves contribute to tumor growth through direct nerve–cancer interactions as well as through modulation of immune responses within the tumor

microenvironment. Understanding these distinct neural roles has been facilitated by landmark studies that reveal the functional importance of neural signaling pathways in pancreatic cancer biology.[7,8,9]

Despite advances in surgery and systemic therapies, pancreatic cancer remains difficult to treat, with a five-year survival rate of approximately 12%. The lack of early diagnostic biomarkers and the tumor's anatomical location continue to impede timely detection. Consequently, there is an urgent need to expand therapeutic strategies beyond conventional approaches. Targeting neural components and tumor–nerve crosstalk represents a promising and emerging avenue for improving cancer control, alleviating pain, and enhancing patient quality of life.

Materials and Methods:

We conducted a targeted literature review of peer-reviewed studies describing neural remodeling, perineural invasion, and neuropathic changes in pancreatic ductal adenocarcinoma, including mechanistic insights from both clinical and preclinical research. Primary databases searched included PubMed, Web of Science, and Scopus using terms related to pancreatic cancer and neural interactions, guided by major existing reviews and experimental studies (Deborde et al.; Wang et al.).

Discussion (example citation style):

Perineural invasion is a defining histopathological feature of PDAC associated with pain and poor survival, driven by reciprocal neuro-tumor signaling involving neurotrophins, chemokines, and glial cells.

Schwann cells dynamically interact with cancer cells to facilitate invasion and may modulate neural plasticity through pathways such as TGFβ and NGF signaling. Moreover, neural remodeling and neuroimmune crosstalk have been implicated in tumor-associated cachexia and central sensitization of pain.

Chemotherapy-induced peripheral neuropathy represents an additional and clinically significant source of neural dysfunction in pancreatic cancer. Neurotoxic chemotherapeutic agents commonly used in treatment regimens can cause long-lasting peripheral nerve damage and cognitive impairment, limiting therapeutic dosing and negatively affecting quality of life. Importantly, chemotherapy-induced neuropathy may interact with pre-existing tumor-associated neural alterations, further exacerbating pain and neurological symptoms.

Collectively, these findings underscore the concept that pancreatic cancer is a nerve-dependent disease, influenced by sympathetic, parasympathetic, and sensory neural inputs. Nerves not only regulate tumor cell behavior directly but also

modulate immune responses within the tumor microenvironment. From a clinical perspective, these insights open new avenues for therapeutic intervention. Targeting tumor–nerve crosstalk, neural inflammation, or neurotrophic signaling pathways may complement existing treatments by suppressing tumor progression, alleviating pain, and reducing treatment-related neuropathy.

In conclusion

In conclusion, understanding the complex interplay between pancreatic cancer and the nervous system provides a unifying framework that integrates tumor biology, symptom generation, and treatment toxicity. Future studies aimed at translating these mechanistic insights into nerve-based or neuro-modulatory therapies may significantly improve outcomes and quality of life for patients with pancreatic cancer.

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