Review

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Review

Neuroimmune Interactions in Pancreatic Cancer

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Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive primary malignancy, and recent technological advances in surgery have opened up more possibilities for surgical treatment. Novel data show that diverse immune and neural components play essential roles in the aggressive behavior of PDAC. Recent studies have shown that neural invasion, neural plasticity, and altered innervation of autonomic nerve fibers are involved in pancreatic neuropathy in PDAC patients and have clarified the functional structure of the nerves innervating pancreatic draining lymph nodes. Notably, research on the pathogenesis and therapeutic options for treating PDAC from the viewpoint of interactions of the neuroimmune network is at the cutting edge. In this review, we present a special focus on neuroimmune interactions that highlight the current state of knowledge and future challenges concerning the reciprocal relationship between the immune system and nervous system in PDAC. Understanding the molecular events governing the pancreatic neuroimmune signaling axes will enhance our knowledge of physiology and may provide novel therapeutic targets for treating PDAC.

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1. Introduction

The nervous system and immune system communicate throughout the body and in the central nervous system, which can recognize danger simultaneously and respond in both a simultaneous and coordinated fashion to regulate tissue and organ function in homeostasis and diseases [1–5]. However, the field of neuroimmunology has undergone a recent renaissance, and evidence suggests that nervous system and immune system communication is far more complex than previously realized.

Neuroimmunology studies to date have tended to focus on interactions between nerves and immune systems at the local level. Peripheral neuroimmune interactions critically regulate systemic and local tissue immunity. Novel data show that the immune system and nervous system play mutual roles in the body and are essential in immune, metabolism-related, neoplastic, and other diseases [6–8].

As an organ associated with neuroimmunity, the pancreas is densely innervated by a complex network of neurons that coordinate critical physiological functions. In addition, pancreatic draining lymph nodes have pancreatic innervation and exert some immunomodulatory effects [9]. Notably, research on the pathogenesis and therapeutic options for treating pancreatic ductal adenocarcinoma (PDAC), including recently identified local forms, from the viewpoint of crosstalk of the neuroimmune network and intervention techniques is at the cutting edge. Current evidence reveals the neuroimmune crosstalk occurring in PDAC, explaining the role of interactions between different

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types of nerve and immune cells in PDAC in terms of tumor formation, development, and metastasis [10–12].

In this review, we focus specifically on neuroimmune interactions associated with PDAC, aiming to elucidate the value of neuroimmune crosstalk in PDAC pathogenesis and intervention through the effects of different types of neural and immune cells on PDAC.

2. Neuroanatomy in the Pancreas and Draining Lymph Nodes

The anatomy of pancreatic innervation includes sympathetic efferent, parasympathetic efferent, vagal afferent, spinal afferent, and enteropancreatic innervation [13]. In the human pancreas, these different types of nerves have distinct innervation characteristics. Using three-dimensional imaging, Chien and colleagues revealed that nerve fibers positive for substance P as the afferent nerve are located at the base of the interlobular duct and that nerve fibers positive for vesicular acetylcholine transporter and tyrosine hydroxylase as the efferent nerve exist in the periacinar and perivascular spaces, which reach the islet along a blood vessel [14]. Neurons and glial networks enter the islet core, and sympathetic and parasympathetic nerves reside in the immediate microenvironment [15]. However, few parasympathetic cholinergic axons innervate the islets in humans, and the sympathetic nerves entering the islets preferentially innervate the vascular smooth muscle cells in islets [16]. The sympathetic nervous system constricts blood vessels in many parts of the body to ensure the stability of the circulatory system under special circumstances [16]. Nerves not only extend to pancreatic parenchyma cells but also some mesenchymal cells. However, further studies are needed to confirm the existence and function of unique connections between nerve cells and various mesenchymal cells.

More recently, novel findings on the functional structure of nerves innervating pancreatic draining lymph nodes have been reported in terms of neuroimmune regulation [9]. Lymph nodes serve as immune organs to filter lymphatic fluid and initiate local adaptive immune responses. The peripheral nervous system communicates specifically with the immune system through local interactions that provide the structural basis for complex immune and neural response networks [17]. By identifying a molecularly distinct and heterogeneous population of sensory neurons with the capacity to affect lymph node function and homeostasis, Huang et al. recently established lymph nodes as a point of convergence between the sensory nervous system and the immune system [18].

Regarding experimental animals, the presence of norepinephrine innervation in the popliteal and mesenteric lymph nodes of mice has long been detected by fluorescein histochemistry [19]. Sympathetic nerves, including perivascular and discrete structures, are observed in human inguinal lymph nodes, and the number of sympathetic nerves varies between compartments and between and within individuals [20]. According to a study of human pancreas specimens, sympathetic innervation of secondary lymphoid organs, such as lymph nodes, varies by species and is influenced by certain physiological or pathological conditions [21]. By placing a suction electrode and recording a field action potential with microelectrodes, projection of pancreatic nerves to mouse lymph nodes was demonstrated by stimulation of pancreatic nerves [9].

3. Neural Plasticity in PDAC

Neural plasticity is an inherent feature of PDAC and involves neuronal activation at the peripheral, spinal and supraspinal levels [22]. Sympathetic nerve innervation of the pancreas is significantly lower in patients with PDAC than in patients with a healthy pancreas, and the number of sympathetic fibers in PDAC patients without nerve invasion is markedly higher than in those with nerve invasion [23]. In contrast, there is no significant change in parasympathetic or cholinergic nerve distribution [23].

In terms of spatial variation in the pancreatic nerve distribution, increased nerve density and hypertrophy compared with those in the normal pancreas are typical features of PDAC [24]. The density of intrapancreatic nerves in patients with PDAC tends to decrease toward the center of the tumor [2]. In mice, nerve hypertrophy and infiltration gradually follow the progression of PDAC,

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and hypertrophy of the nerve is associated with fibrosis of the corresponding area and atrophy of pancreatic acinar cells [25]. The mean percentage of sympathetic nerve fibers per nerve in the pancreas of PDAC patients is significantly lower than that in the pancreas of healthy patients [23], which may be partly explained by a decrease in the number or volume of sympathetic nerves or both. In patients with PDAC, increased nerve size is associated with decreased numbers of cholinergic and adrenergic nerve fibers and enhanced neural nesting immunoreactivity [23]. Indeed, there is a correlation between the volume and number of pancreatic nerves. In addition to the neurological changes described above, changes in neurotrophic factor expression occur prior to tumor formation, and the nervous system is involved in all PDAC processes, including the period before cancer development [25].

4. Neuroimmune Crosstalk in PDAC

Neuroimmune crosstalk, which can serve as a crucial immunomodulatory hub, has been reported in both healthy and disease states [8,26–28]. Emerging evidence suggests that the somatosensory and autonomic nervous systems play an active role in host defense via direct regulation of immunological and inflammatory responses in the periphery [29,30]. For instance, enteric neurons can reduce surgery-induced intestinal inflammation and prevent postoperative ileus through regulation of mucosal macrophages [31]. Nerve fibers of mouse lymph nodes have close contacts or associations with immune cells, including dendritic cells, macrophages, and T or B lymphocytes [17]. Moreover, the impact of the neural system on immune function and immune cells via cytokine and trophic factor secretion can influence endogenous neural stem cell proliferation, differentiation and migration [29,30,32]. For example, enteric neurons maintain the development of muscularis macrophages in a steady state by secreting colony stimulatory factor 1; reciprocally, muscularis macrophages can activate intestinal neurons expressing bone morphogenetic protein receptors by secreting bone morphogenetic protein 2[33].

Neuroimmune regulation is related to neoplastic diseases and plays a specific role in the occurrence and development of tumors. In breast cancer, tumor-specific sympathetic denervation downregulates expression of immune checkpoint molecules, including programmed death-1 and programmed death ligand-1, on $CD4^+$ or $CD8^+$ T cells and upregulates that of interferon-γ on $CD4^+$ or $CD8^+$ cells, which have an active effector phenotype [34]. The sympathetic nervous system can maintain the inflammatory microenvironment and promote the occurrence of hepatocellular carcinoma by activating the a1-adrenergic receptors of Kupffer cells [35].

PDAC is a highly aggressive tumor, with a five-year survival rate of only approximately 10%[36]. Pathological and immunohistochemical examinations of PDAC tissue have revealed specific nervous and immune system features. The tumor microenvironment is closely related to neoplastic development [37–41], and neural signals play a role in the tumor microenvironment [42]. Neurotropism is an important histological feature of PDAC that is associated with frequent neurological invasion [43]. In addition, perineural invasion is a common feature of PDAC and is associated with impaired immune responses [11].

In pancreatic cancer, nerves are significantly infiltrated by cytotoxic T lymphocytes, macrophages, and mast cells, which account for 35%, 39%, and 21%, respectively, of all perineural inflammatory cells [5]. Perineural invasion can induce neuronal damage and inflammation [44]. Colocalization of nerve and immune cells may affect nerve and immune functions, and this neuroimmune regulation may lead to changes in disease. Nerves can regulate tumor growth in ways that affect tumor metabolism. For example, nerves promote PDAC growth in nutrient-deficient environments by releasing substances necessary for tumor growth, such as serine [45]. The neuroimmune interactions occurring in PDAC at the peripheral nerve level, including the regulation of immune cells and sympathetic, parasympathetic and sensory nerves, are summarized in Figure 1. Despite the promising achievements of tumor immunotherapy in many tumor types, it has not been very successfully applied in PDAC treatment [46]. Determining the mechanisms of neuroimmune

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regulation in pancreatic cancer may facilitate the progress of tumor immunotherapy for pancreatic cancer treatment.

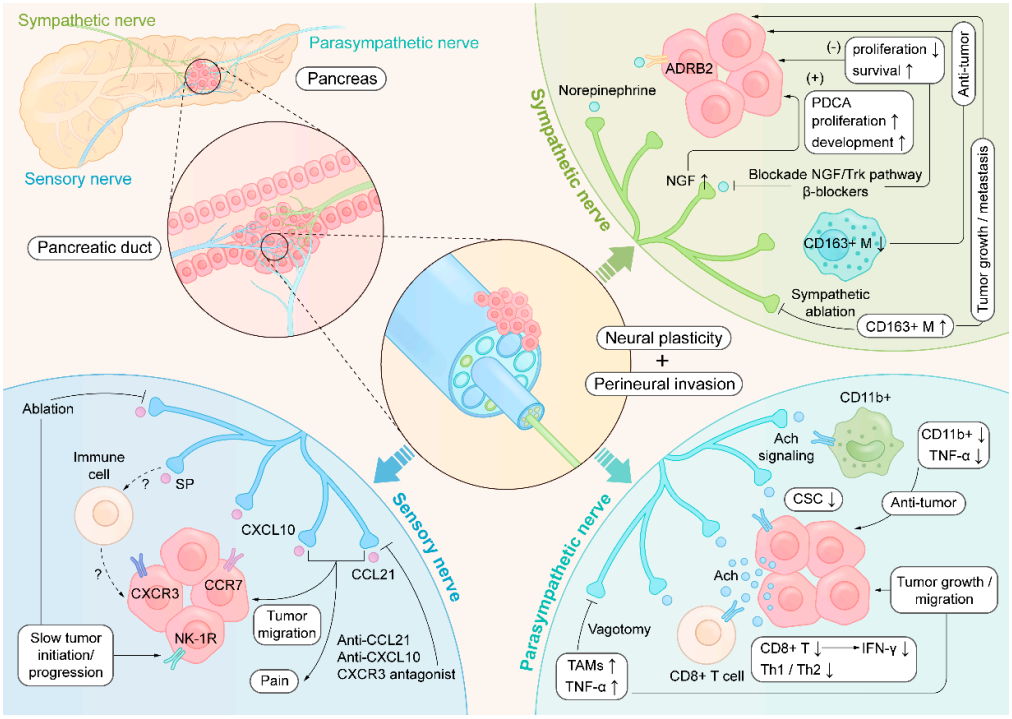

Figure 1. Neuroimmune interactions and interventions in pancreatic ductal adenocarcinoma at the peripheral nerve level. Ach, acetylcholine; ADRB2, adrenoceptor beta 2; CSC, cancer stem cell; IFN-γ, interferon-γ; PDAC, pancreatic ductal adenocarcinoma; SP, substance P; TAMs, tumor-associated macrophages; TNF-α, tumor necrosis factor-α; NGF, nerve growth factor; NK-1R, neurokinin-1 receptor.

4.1. Sympathetic Nerve

Different interactions between a variety of nerves and immune cells in the pancreas may produce different effects. Sympathetic nerves are known to promote prostate cancer, breast cancer and melanoma [1]. In the pancreas, sympathetic nervous system/β-adrenoceptor signaling promotes tumor growth [47], and neuromodulation contributes to PDAC at all stages, even before cancer appears [48]. Recent findings have provided insights into the mechanisms by which the sympathetic nervous system exerts its cancer-protective effects in a mouse model of PDAC, but these effects are not caused by nerves acting alone [10]. Indeed, research has demonstrated that sympathetic axons slow PDAC progression by locally inhibiting $CD163^{+}$ macrophage subsets at the lesion site; ablation of innervated sympathetic nerves increases tumor growth and spread, which supports use of CD163+ macrophages as mediators of the protumoral effect of sympathetic resection in PDAC [10]. In melanoma-bearing mice, beta-adrenergic receptor blockers increase the frequency of effector CD8+ T cells in tumors and reduce expression of programmed death receptor-1[49].

4.2. Parasympathetic Nerves

The neural effects of sympathetic and parasympathetic nerves may be modulated by β-adrenergic and muscarinic receptors, respectively [1]. Recent research suggests that parasympathetic nervous system input inhibits primary and secondary tumorigenesis of PDAC through cholinergic signaling and that stimulation of muscarinic receptors may be helpful in treatment of PDAC [12]. In mice with established PDAC, stimulation of muscarinic type 1 receptors can suppress the cancer stem cell compartment, CD11b+ myeloid cells, tumor necrosis factor α (TNF-α) levels, and metastatic growth in the liver. Vagotomy significantly increases the number of tumor-associated macrophages

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and levels of TNF-α in tumors, promoting tumor growth and reducing survival in a murine pancreatic cancer model [50].

4.3. Sensory Nerves

In genetically engineered PDAC mouse models, sensory innervation increases during pancreatic intraepithelial neoplasia formation and increases further during cancer progression [25]. The chemokines CCL21 and CXCL10, which originate from sensory neurons, promote PDAC metastasis through their receptors CCR7 and CXCR3, respectively [51]. Ablation of sensory neurons in genetic models of PDAC delays formation of pancreatic intraepithelial neoplasia and ultimately prolongs survival [44]. In addition to nerve cells, Schwann cells of peripheral nerves are activated in the preneoplastic stage of cancer, possess strong affinity for cancer cells and initiate nerve cancer cell interactions [52,53]. TIMP1 from pancreatic cancer cells stimulates Schwann cells and promotes peripheral nerve invasion, and TIMP1 knockdown can suppress peripheral nerve invasion [54].

Major depressive disorder is four times more common in cancer patients than in the general population [55]. Psychosocial stress activates the sympathetic nervous system, hypothalamic–pituitary–adrenal axis, and neuroendocrine axis and subsequently regulates inflammatory responses through immune cells [56]. In cancer patients, psychosocial stress promotes inflammation and oxidative stress, decreased immunosurveillance, and dysfunctional activation of the autonomic nervous system and the hypothalamic–pituitary–adrenal axis [55]. Human and animal studies have shown that sympathetic and neuroendocrine responses to psychosocial stress significantly influence cancer by regulating inflammatory mediators [56]. For instance, psychological intervention in regional breast cancer patients enhance natural killer cell cytotoxicity and T-cell proliferation and reduce the risk of death after recurrence [57].

5. Neuroimmune Regulation Intervention

With advances in surgical techniques, surgical treatment can be used for an increasing number of patients with PDAC [58]. In addition, surgical denervation has long been reported for pain management in patients with PDAC who cannot undergo surgical tumor removal [59]. To date, many intervention studies related to neuroimmune interactions have been performed, and some of the intervention methods related to PDAC are summarized in Figure 1. In clinical practice, beta-adrenergic receptor blockers, such as propranolol, are the most commonly used drugs to attenuate sympathetic adrenergic function. Patients with PDAC administered beta-adrenergic receptor blockers had a lower cancer-specific mortality rate than did those not given these drugs [60]. Compared with conventional receptor blocker drugs, use of a liposome nanomedicine system to administer propranolol hydrochloride can avoid the adverse effects caused by inhibition of nontargeted adrenergic neural activity [61]. Furthermore, it has considerable therapeutic effects on PDAC, prostate cancer, and melanoma, with increased safety and efficiency [61].

There are very precise optogenetic and pharmacogenetic methods that allow neurons to be manipulated in very specific ways [62]. As a genetic local neuroengineering technology, adeno-associated virus vectors designed to carry transgenes downstream of neuron fiber type-specific promoters can stimulate tumor immunity, such as increased effector helper or cytotoxic T cells in primary tumor tissue, and achieve greater tumor suppression efficacy than administration of beta-adrenergic receptor blockers [34]. These methods may be developed for the pancreas in the future to achieve desired results. In general, pancreatic neuroimmune regulation will develop in the direction of less trauma, strong targeting and convenient use.

In addition to use of systemic drugs, there are many methods for direct neurological intervention, including neurotomy, nerve ablation, and nerve block. Perineural invasion is associated with an immunosuppressive microenvironment in PDAC, and intervention involving perineural invasion with bilateral subdiaphragmatic vagotomy is associated with increased $CD8^+$ T cells, an increased Th1/Th2 ratio, and improved survival [11]. In contrast to surgery, ultrasound-guided celiac plexus block and neurolysis are used to relieve and treat pain in patients with PDAC [63].

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In the past few decades, electrical stimulation therapy has attracted considerable attention as a new therapeutic method. The electric field enhances keratinocyte migration, strengthens immune defense, and improves mitochondrial function, and a weak electric field can be safe and has antibacterial effects on the human body [64]. Compared with traditional drugs, which require systematic administration and a certain amount of time for effect depending on the administration, electrical stimulation can act directly on nerve bundles to produce rapid effects [65]. As a bioelectric therapy, stimulation of the vagus nerve in epilepsy patients with an implanted device reduced levels of TNF, interleukin-1β, and interleukin-6 in peripheral blood [66]. More recently, electrical stimulation of the pancreatic nerve was shown to prevent autoimmune diabetes by inhibiting migration of diabetogenic T cells from pancreatic draining lymph nodes to islets, resulting in less severe insulitis [9].

In addition to confirming the research value, some experimental teams have obtained inconsistent results after repeating the above experiment [67]. Moreover, it should be kept in mind that stimulation of the vagus nerve involves afferent and efferent nerves and controls multiple tissues and organs; in fact, stimulation of the vagus nerve not only causes the desired therapeutic effects but also nerve stimulus-related side effects [9]. Therefore, enhancing targeting of electrical stimulation therapy to reduce side effects can improve the clinical application prospects of electrical stimulation. However, there are still many problems to be solved, such as the design of the electrode to stimulate the pancreatic nerve, the setting of electrical stimulation parameters, and the method of electrode implantation.

6. Concluding Remarks and Future Perspectives

The findings of neuroimmune network crosstalk and intervention techniques in PDAC open up a fertile area for detailed studies that have broad translational implications. Much of the information obtained to date involves the structural plasticity of pancreatic nerves, specifically under conditions of inflammation or cancer. Most previous studies have focused on peripheral neuroimmune crosstalk and aimed to understand the reciprocal relationship between the immune system and nervous system during pancreatic neoplasms. More recently, novel data on the functional structure of nerves innervating pancreatic draining lymph nodes have revealed neuronal communication with stromal and immune cells. Furthermore, recent studies have highlighted interventions targeting pancreatic neuroimmune signaling axes and presented an emerging avenue for treatment of pancreatic diseases. Neuroimmune interactions at the peripheral nerve level in PDAC patients, including interactions in the pancreas and draining lymph nodes, should be explored in depth to elucidate their implications, which will help scholars and clinicians to recognize and manage PDAC patients from a new perspective.

In general, the molecular mechanisms underlying the dynamic pathological conditions of neuroimmune crosstalk are poorly understood. Further research on the internal links and mechanisms of neuroimmune regulation and intervention in pancreatic physiology and pathophysiology will be helpful for understanding the pancreas and PDAC and provides a basis for diagnosis and treatment. Exciting areas for future research include gaining a more comprehensive understanding of the anatomical, molecular, and cellular basis of neuroimmune crosstalk in PDAC; revealing the innervation established during development and homeostasis maintenance of the pancreas; clarifying how neuronal communication to stromal and immune cells of the lymphatic vasculature is mediated [68]; identifying nerve-derived factors, in addition to neurotransmitters and immunomodulatory factors; and elucidating the cell types that are directly targeted by nerves that mediate effects on PDAC. Technological advances in chemical genetic tools, optogenetics and single-cell sequencing offer new opportunities to reveal the anatomical, molecular and cellular profiles of specific neuronal and immune subtypes projecting to the pancreas and associated circuits.

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Abbreviations

The following abbreviations are used in this manuscript:

PDAC	Pancreatic ductal adenocarcinoma
Ach	Acetylcholine
ADRB2	Adrenoceptor beta 2
CSC	Cancer stem cell
IFN-γ	Interferon-γ
SP	Substance P
TAMs	Tumor-associated macrophages
TNF-α	Tumor necrosis factor-α
NGF	Nerve growth factor
NK-1R	Neurokinin-1 receptor

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