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REVIEW ARTICLE

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Roles of the nervous system in pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), with its extremely poor prognosis, presents a substantial health problem worldwide. Outcomes have improved thanks to progress in surgical technique, chemotherapy, pre-/postoperative management, and centralization of patient care to high-volume centers. However, our goals are yet to be met. Recently, exome sequencing using PDAC surgical specimens has demonstrated that the most frequently altered genes were the axon guidance genes, indicating involvement of the nervous system in PDAC carcinogenesis. Moreover, perineural invasion has been widely identified as one poor prognostic factor. The combination of innovative technologies and extensive clinician experience with the nervous system come together here to create a new treatment option. However, evidence has emerged that suggests that the relationship between cancer and nerves in PDAC, the underlying mechanism, is not fully understood. In an attempt to tackle this lethal cancer, this review summarizes the anatomy and physiology of the pancreas and discusses the role of the nervous system in the pathophysiology of PDAC.

KEYWORDS

axon guidance, nerve growth factors, neurotrophic tyrosine kinase receptor, pancreatic neoplasms, tumor microenvironment

1 | INTRODUCTION

Pancreatic cancer has the poorest prognosis of any cancer. Pancreatic cancer is the third leading cause of cancer-related mortality in the United States, with a 5-year overall survival of 9%; an estimated 47 050 Americans will die of the disease in 2020.[1] Globally, in 2018, 458 918 pancreatic cancer diagnoses were made, comprising 2.5% of worldwide cancer cases, and 432 242 deaths contributed to 4.5% of worldwide cancer-related deaths.[2] Approximately 95% of pancreatic cancers originate from exocrine cells, most commonly pancreatic ductal adenocarcinomas (PDAC).[3] Endocrine pancreatic cancers generally have a more favorable prognosis.[4] Ductal adenocarcinoma is the most common malignancy of the pancreas. Accordingly, this tumor presents a substantial health problem worldwide.[5,6]

Through exome sequencing of PDAC surgical specimens, in a very interesting study, Biankin et al demonstrated that the axon guidance gene family was the most frequently altered gene family.[7] Their findings suggest the potential involvement of the nervous system in PDAC carcinogenesis.

In clinical pancreatic cancer management, perineural invasion (PNI) is the most significant nerve-related problem. PNI has been characterized as the neoplastic invasion of tumor cells into or surrounding the nerves.[8-12] It is a characteristic feature of PDAC associated with a poor prognosis, tumor recurrence, and pain generation.[13-16] The prevalence of PNI in PDAC is far higher than in other

gastrointestinal malignancies.[8,17-19] Furthermore, the PNI severity is more severe compared to other gastrointestinal malignancies.[17] However, it remains unclear why PDAC is associated with a higher incidence of PNI.

The inhibition of PNI would have the potential for improving prognosis in patients with PDAC. However, neither the underlying mechanism of PNI nor the crosstalk between cancer cells and nerves within PNI has been fully understood. Furthermore, the role of nerves in PDAC initiation and progression has remained unclear. It is assumed that the elucidation of these biological phenomena will provide new treatment strategies targeting nerve-cancer signaling that prevent PNI and improve survival in PDAC patients.

In this review, we describe a brief overview of the anatomy and physiology of the pancreas. Then, we discuss novel possibilities for the role of nerves in PDAC, mainly focusing on nerve-cancer interactions.

2 | CLINICAL ANATOMY OF THE PERIPANCREATIC NERVE PLEXUS

The pancreas has an abundant nerve supply. Many nerve branches supply the pancreas and form several nerve plexuses.[20-25] In the General Rules for the Study of Pancreatic Cancer edited by the Japan Pancreatic Society,[23] these extrapancreatic nerve branches are divided into seven plexuses as follows: the pancreatic head nerve plexus I (PLphI), the pancreatic head nerve plexus II (PLphII), the superior mesenteric nerve plexus (PLsma), the common hepatic nerve plexus (PLcha), the hepatoduodenal ligament nerve plexus (PLhdl), the splenic artery nerve plexus (PLspa), and the celiac plexus (PLce).

Figure 1 shows the schema of the nervous system around the pancreas. The nerves serving the pancreas head mainly derive from the celiac plexus. They are divided into the anterior hepatic plexus running along the common hepatic artery, and the posterior hepatic plexus running through the depths and behind the portal venous system.[20] Innervation of the pancreas head is largely thanks to the posterior hepatic plexus originating from the right celiac ganglion, which is equivalent to the "pancreatic head nerve plexus I" reported by Yoshioka and Wakabayashi.[20,26]

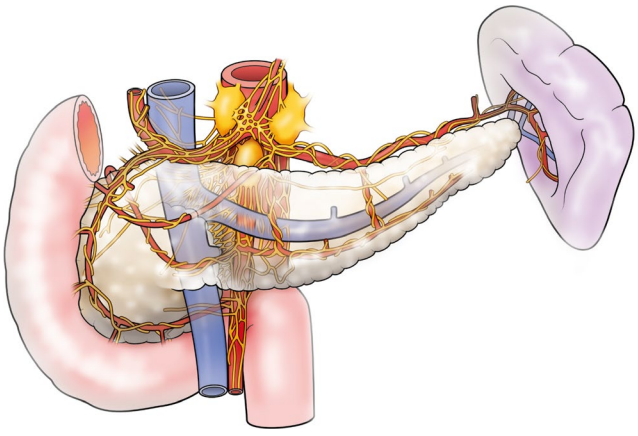

FIGURE 1 The schema of the nervous system around the pancreas. This figure based on Ref. [14,20,23,24,25]

The innervation of the uncinate process of the pancreas originates from the superior mesenteric plexus. The nerve is divided into two pathways: the direct pathway and the accompanying pathway. Pancreatic head nerve plexus II from the superior mesenteric arterial plexus directly entering the uncinate process is considered the direct pathway. The accompanying pathway is the nerve along the inferior pancreaticoduodenal artery.[20]

The innervation of the body and tail of the pancreas is divided into two routes. One route, derived from the splenic plexus, branches into the body and tail directly or passes along the great pancreatic artery and the dorsal pancreatic artery. The other originates from the celiac plexus and directly enters the pancreatic parenchyma at the neck of the pancreas. One branch of the celiac plexus runs to the parenchyma along the inferior pancreatic artery and is distributed mainly into the lower body and tail of the pancreas. This branch achieves communication in the periphery with the branch of the splenic plexus. The other celiac plexus branch is distributed around the pancreatic duct without the accompanying artery.[20]

Those peripancreatic nerve plexuses involved in the sensory nerve and autonomic nervous system include the sympathetic, parasympathetic, and enteric divisions.

3 | THE INNERVATION OF THE PANCREAS

The pancreas consists of two functional components. The exocrine pancreas, occupying a major portion of the pancreas, consists of acinar cells and ductal cells. This part releases digestive enzymes and bicarbonate into the duodenum. The endocrine pancreas is organized into the islets of Langerhans. The endocrine pancreas secretes hormones, including insulin, glucagon, ghrelin, pancreatic polypeptide, and somatostatin.[27,28] Both components of the pancreas are innervated by the autonomic nervous system, and regulated by the separate pathways for normal activity.

3.1 | Parasympathetic neurons

Preganglionic parasympathetic neurons originate from the dorsal motor nucleus of the vagus.[29-31] This activates parasympathetic postganglionic neurons in the pancreatic ganglia, primarily via activation of nicotinic acetylcholine receptors.[32,33] Various neurotransmitters and neuromodulators can regulate these transmissions between pre- and postganglionic neurons.[32,34] The distribution of parasympathetic neurons is wider than that of sympathetic neurons, with some overlapping regions.[32] The postganglionic neurons release several neurotransmitters, which are excitatory or inhibitory depending upon the receptor.[33] One typical neurotransmitter is acetylcholine (Ach), which binds to muscarinic receptors and produces a tonic input.[35] Nitric oxide

(NO), vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide, and pituitary adenylate cyclase-activating polypeptide (PACAP) are also released from the parasympathetic nerve.[30,32,36] Parasympathetic innervation plays a role in the regulation of pancreatic function.[37-39] Activation of the parasympathetic nerve mainly leads to excitatory input, which results in increases of both exocrine and endocrine secretion.[40-46]

3.2 | Sympathetic neurons

Preganglionic sympathetic neurons originate from the lower thoracic and upper lumbar segments of the spinal cord.[29,31,47-49] They exit the spinal cord through the ventral roots and reach either the paravertebral ganglia of the sympathetic chain or the celiac and mesenteric ganglia.[28,29,32,33,35] The postganglionic sympathetic nerve terminates at the intrapancreatic ganglia, islets, and pancreatic blood vessels.[29,32,50] Although it is modest compared to islets and blood vessels, some sympathetic nerves project to acinar cells and ducts.[29,51] They release various neurotransmitters, including norepinephrine (NE), galanin, and neuropeptide Y.[36,52,53] Sympathetic nerves primarily decrease plasma insulin levels.[54-57] Conversely, stimulation of the sympathetic nerves increases glucagon secretion.[54,57-60] These findings suggest that the overall effect of the sympathetic nerves on endocrine function is to maintain glycemic levels during stressful conditions.[33] The sympathetic nerve primarily inhibits pancreatic exocrine secretion; however, what the definitive effect is remains controversial.[32,33]

3.3 | Enteric neurons

The enteric nervous system is the third division of the autonomic nervous system.[61] The enteric nerve from within the gastric antrum wall and the proximal duodenum wall reaches the intrapancreatic ganglia.[62,63] The enteric fiber can release multiple neurotransmitters and neuromodulators, including Ach, serotonin, PACAP, and NO.[62,64] Some studies have indicated a relationship between the enteric nerve and pancreatic function.[63,65-67] However, the role of the nerve in controlling the endocrine and exocrine functions in humans is not yet fully understood.

3.4 | Sensory neurons

The sensory nerves of the pancreas reach the central nervous system via both the vagal and spinal routes.[21,31,33,68] Although the central targets of vagal afferents have not been fully established, the nucleus of the solitary tract is the strongest candidate.[21,64] Sympathetic and parasympathetic afferent nerves are capsaicin-sensitive, and contain substance P and calcitonin gene-related peptide, or both.[68-71] Mechanosensitive fibers are primarily associated with blood vessels.[72] Some studies have suggested that sensory nerves may inhibit insulin secretion[73,74] and exocrine secretion.[75] However, the role of sensory nerves on pancreatic functions has not been fully proven.

4 | THREE-DIMENSIONAL MICROSCOPIC FINDINGS OF THE PANCREATIC INNERVATION

Thanks to two innovative technologies, tissue clearing and advanced microscopy, we have been able to distinctly visualize three-dimensional (3D) anatomy and pathology.[76] These technological advances definitely contribute to further organizing knowledge of the pancreatic nerves. Tang et al visualized the neuro-insular network via 3D histology.[77,78] They demonstrated that both the sympathetic and parasympathetic nerves enter the islet and reside in the islet cell's immediate microenvironment. They also found the intrapancreatic ganglia (perilobular and intraparenchymal ganglia) and the islet-ganglionic association around the islets.[78] Intrapancreatic ganglia include pancreatic neurons, glial cells, and extrinsic and intrinsic nerve fibers.[78] These results provide novel insights into human pancreatic disease.

On the other hand, the relationship between the nerves and exocrine components has not been a center of focus. With 3D histology, our colleagues have visualized the nerve fiber networks around the pancreatic acinar cells and duct cells in the human pancreas (Figure 2).

5 | NERVE-CANCER CROSSTALK WITHIN PNI IN PDAC

A century ago, PNI was identified as one of the routes for metastatic spread.[9,10] Recently, our ability to understand the molecular mechanisms behind PNI has become clearer. Several lines of evidence from current studies have caused a paradigm shift in our recognition of PNI. In short, they have indicated that PNI is a metastatic route as well as a critical command center during the progression of PDAC. We next discuss the role of nerves in PDAC. We attempt to clarify how nerves contribute to the pathogenesis of PDAC.

5.1 | Nerve-mediated development and organ patterning in the pancreas

During the initial phase of cancer progression, tumors activate nerve-dependent pathways similar to those in normal development.[79] Thus, we first provide a brief overview of nerve-mediated development and organ patterning. To understand nerve-mediated development and organ patterning in the normal pancreas, research findings using the submandibular gland, which also has acini and ducts, are helpful.[79] During gland development, a variety of cells, including the epithelial, mesenchymal, and stromal cells, secrete

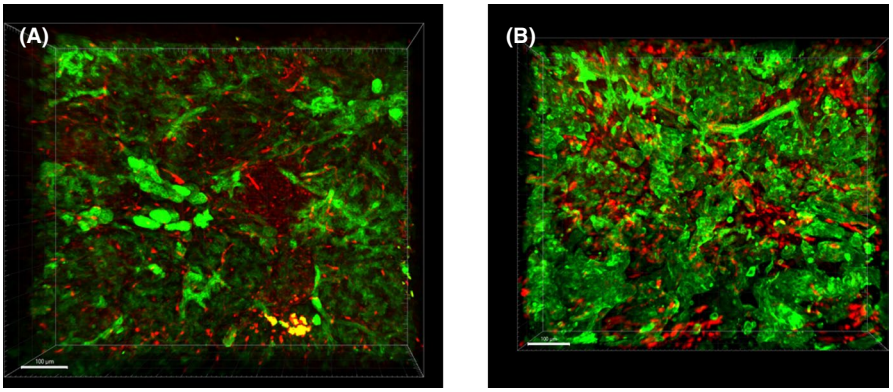

FIGURE 2 Representative 3D image of multicolor immunofluorescent labeling. Comparison of the nerve distribution in the normal pancreas (A) with pancreatic cancer (B). Markers: CK19 (epithelial cells), green; S100 (nerves), red

various neurotrophins to elicit the recruitment of the peripheral nerves. This phase is called the nerve recruitment phase.[79]

To date, several neurotrophins and their cognate receptors have been identified. There are four neurotrophins recognized in humans: the prototypical nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4/5 (NT-4/5).[80] In addition, some polypeptide factors, including ciliary neurotrophic factor (CNTF)[81] and glial cell line-derived neurotrophic factor (GDNF),[82] possess neurotrophic activity.[80] The biological effects of each of the four neurotrophins are mediated through activation of one or more of the three members of the tropomyosin-related kinase (Trk) family of receptor tyrosine kinases (TrkA, TrkB, and TrkC). In addition, all neurotrophins activate the p75 neurotrophin receptor ($p75^{NTR}$), a member of the tumor necrosis factor receptor superfamily.[80] The cognate receptor of GDNF is GDNF family receptor-α2 (GFRα2).[83] Neurotrophin binding to the receptor on nerves leads to retrograde signals that travel from the distal axon to the cell body and dendrites. These signals promote gene expression and axogenesis.[84,85]

After the nerve recruitment phase, parasympathetic nerves initiate ductal epithelial tubulogenesis through VIP signaling.[86] Additionally, parasympathetic nerves also regulate glandular or acinar epithelium growth and patterning through ACh signaling by activating SRY-box 2 (SOX2).[87] On the other hand, sympathetic nerves are necessary for patterning the vasculature in gland development.[88,89] In the developing pancreas, adrenergic innervation is associated with a rapid phase of glandular growth and maturation. Conversely, the deletion of neurotrophin or their receptors leads to the disruption of the glandular architecture.[90,91] In summary, the nerve and nerve-mediated pathways are essential to the development and organ patterning of the pancreas.

5.2 | Vicious cycle between the nervous system and cancer cells

In cancer, to continue to grow and be maintained, tumor cells and the surrounding reactive stroma release neurotrophins to recruit nerves.[79,92] These tumor-derived neurotrophins result in axonogenesis of the autonomic nerve and the sensory nerve.[93] After the nerve recruitment phase in cancer, each nerve contributes to the growth phase of the cancer. Sympathetic nerves generate neovasculature, similar to what happens in tissue development.[94] Through mitosis, parasympathetic nerves activate tumor cells, which starts growth expansion.[95] Parasympathetic nerves also give tumor cells migratory cues for metastasis.[96] Furthermore, cancer cells migrate along the nerve and invade into nerves in response to various mediators released by the peripheral nerves and nerve resident macrophages.[8,93,97-103]

In short, cancer cells themselves create a favorable environment for cancer by modulating neural systems. Unfortunately, these nerve-cancer interactions can cause a fatal vicious cycle in PDAC. Based on characteristic findings, including the abundant nerve supply to the pancreas and the higher frequency and degree of PNI, this lethal downstream spiral in PDAC may be greater than in other cancers, which may be one reason that PDAC has one of the poorest prognoses.

5.3 | Increased nerve density in PDAC specimens

During cancer progression from preneoplastic lesions to cancer, increased nerve density is a significant feature in neoplastic tissue.[94,104] Furthermore, increased nerve density has been found to correlate consistently with more aggressive disease,[105,106] including pancreatic cancer.[107] In the pancreatic intraepithelial neoplasia (PanIN), increased nerve density has been demonstrated.[108,109] Moreover, as expected from the result in PanIN, a drastically increased number and size of intrapancreatic nerves were observed in PDAC.[9,110] This observation is termed pancreatic cancer-associated neural remodeling (PANR).[102,111,112] Several lines of evidence revealed that an increase in nerve density is paralleled by an increase in neurotrophin production.[94,104,108,113] Stopczynski et al reported that neurotrophins as well as their cognate receptors increased early in the development of PDAC.[109] In human PDAC specimens, interestingly, neurotrophin expression was primally within the stromal compartment, not within the epithelial compartment.[114,115] Our 3D image of cleared human PDAC, visualized by Dr Yoshizawa, clearly demonstrated the increased nerve density compared to the normal pancreas, which accurately confirms previous reports (Figure 2).

TABLE 1 Evidence for neural regulation in PDAC

Target	Findings	Ref.
Parasympathetic nerves	Nicotine induces tumor metastasis via the α7nAChR/JAK2/STAT3 downstream signaling cascade	132
	Subdiaphragmatic vagotomy accelerates tumorigenesis Muscarinic agonist suppresses tumorigenesis via MAPK and PI3K/AKT signaling	118
Sympathetic nerves	NE inhibits migratory activity via imbalanced activation of PKC/PLC signaling	133
	Catecholamines promote the secretion of NT, which in turn promotes increased NE and tumor growth	114
	NE promotes PNI via β-AR/PKA/STAT3 signaling	134
Sensory nerves	Ablation of sensory neurons slows initiation and progression	116
	SP induces PNI via NK-1R signaling	135
	Increased sensory innervation and NT linked with disease progression from premalignant stages to cancer	109
	Sensory nerves promote PanIN tumorigenesis via NK-1R signaling	108
NT	GDNF/GFRα1-RET signaling in a paracrine manner promotes PNI via MAPK	99
	GDNF/GFRα1-RET signaling derived from endoneurial macrophages promotes PNI via MAPK/PI3K	136
	nerve-released GFRα1 enhances PNI through GDNF/RET signaling	97
	NRTN/GFRα2 signaling derived from tumor cells promotes invasiveness	137
	Artemin/GFRα3-RET signaling promotes cancer invasion	138
	Schwann cells are chemoattracted to cancer cells via NGF/$p75^{NTR}$ interaction	139
	NGF/TrkA expression is associated with PNI	140
Other factors	SDC-2 expression is associated with PNI	141
	PSCs affected by paracrine SHH signaling promote PNI	142
	TGFβ/SMAD signaling derived from Schwann cells enhance aggressiveness and PNI	102
	Axon guidance factor SLIT2/ROBO signaling inhibits PNI and metastasis	121
	Axon guidance factor SEMA3/PLXNA1 promotes tumor dissemination	143
	Axon guidance factor SEMA3D/PLXND1 induces tumor invasion	11,120

Abbreviations: Ach, acetylcholine; AKT, serine/threonine kinase or protein kinase B; GDNF, glial cell-derived neurotrophic factor; GFRα, GDNF family receptor-α; JAK2, janus kinase 2; MAPK, mitogen-activated protein kinase; nAChR, nicotinic acetylcholine receptor; NE, norepinephrine; NGF, nerve growth factor; NK-1R, neurokinin-1 receptor; NRTN, neurturin; NT, neurotrophin; PanIN, pancreatic intraepithelial neoplasms; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; PLXN, plexin; PNI, perineural invasion; PSCs, pancreatic stellate cells; RET, Ret proto-oncogene; ROBO, roundabout; SDC, syndecan; SHH, Sonic Hedgehog; SLIT2, slit guidance ligand 2; SP, substance P; STAT3, signal transducer and activator of transcription 3; TGFβ, transforming growth factor beta; Trk, tropomyosin-related kinase.

5.4 | Evidence for neural modulation in PDAC

To date, there have been several lines of evidence for the neural modulation effect in PDAC (Table 1). Furthermore, neural modulation, by the denervation of the vagus nerve or sensory nerves, would potentially inhibit progression from the PanIN stage to PDAC.[108,116-119] Targeting these signaling pathways may prove useful in the treatment of PDAC.

Regarding axon guidance molecules, there have been some findings of semaphorin and its receptors, plexin. Jurcak et al demonstrated that a PNI mechanism is associated with the semaphorin and plexin gene family in PDAC using mice.[11] They further reported increased levels of semaphorin and plexin in human PDAC specimens associated with PNI. Moreover, human PDAC semaphorin expression is associated with poor survival and metastasis.[120] These results suggest that strategies to disrupt the axon guidance pathway

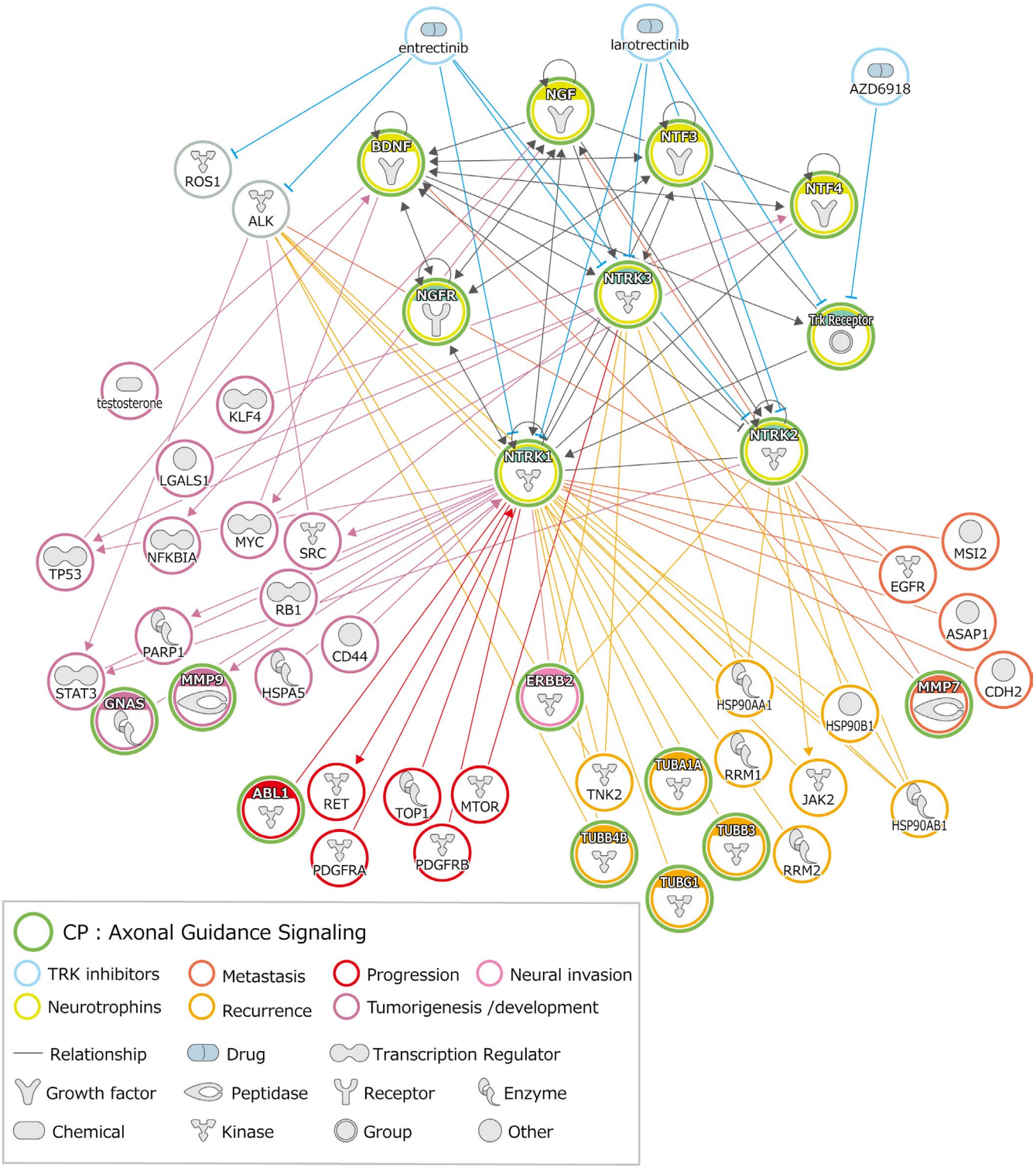

FIGURE 3 Targeting neurotrophins is one candidate for a new treatment strategy for PDAC. We retrieved associated molecules from QIAGEN Ingenuity Pathway Analysis. This network was generated, mainly focusing on TRK, through the use of QIAGEN Ingenuity Pathway Analysis. Direct interactions are shown in this network (excluding indirect interactions). The molecules with the green outline are components of the canonical pathway of axon guidance signaling. The nodes filled in with yellow are neurotrophins, their receptors. Emerging evidence has shown that TRK inhibitors (blue) link together with the yellow nodes (blue arrow lines). Furthermore, we have delineated the molecules of axon guidance signaling, which previously have demonstrated a direct relationship to not only cancer growth but also neurotrophins and their receptors. This network reveals that neurotrophins and their receptors are linked to PDAC progression via various molecules and signaling pathways. The established network reveals that several tropomyosin receptor kinase inhibitors would have anti-cancer effects by suppressing the neurotrophin-related pathways in PDAC

mediated by semaphorin might be developed to slow the progression of PDAC. However, SLIT2/ROBO signaling, one of the axon guidance factors, inhibits PNI and metastasis in PDAC.[121] When considering this conflicting information together, it becomes evident that the role of the axon guidance molecules in PDAC is complicated. More precise characterization is needed to explore new pharmacological approaches targeting molecules.

Tropomyosin receptor kinase (TRK) has been focused on as a new treatment target, because there are actionable inhibitors such as larotrectinib and entrectinib.[122-125] To visualize the role of TRK and the entire relationship with PDAC, we generated a TRK-related network through the use of QIAGEN Ingenuity Pathway Analysis[126] (Figure 3). The evidence that emerged has demonstrated the efficacy of TRK inhibitor in patients with the neurotrophic tyrosine receptor kinase (NTRK) gene fusion-positive.[123,127,128] Although rare, NTRK gene fusions are identified as oncogenic drivers in <1% of PDAC cases,[122,129-131] thus providing a potential treatment target.

6 | FUTURE DIRECTIONS

Based on several lines of evidence elucidated here, what we next want to find out is how neural regulation progresses after curative surgery. Because we have generally performed peripancreatic nerve plexus dissection, a better understanding of how nerve dissection affects the remnant pancreas and tumor microenvironment is highly significant to preventing local recurrence after curative surgery.

Unfortunately, there has not been a clinical or experimental study to assess the effect of residual nerves on tumor recurrence after curative surgery. Based on the previous reports, we can speculate that residual nerves induced/activated by cancer cells could continue to stimulate oncogenesis, cancer growth, and cancer progression even after R0 resection. Furthermore, an immune system modified by tumor-induced nerves could also contribute to increase cancer growth.[93] We really want to know whether the modification applied to the nerve by the switch from cancer cells is reversible or irreversible. If this modification remains irreversible even after R0 resection and promotes postoperative recurrence, we need to inhibit the nerve-induced positive regulation in cancer growth. For that purpose, potential therapeutic options would be based on stopping aberrant tumor neurogenesis and disrupting communication among cancer cells, leukocytes, and neurons.

Innovative pharmacological strategies targeting the nervous system and neurotrophins may improve the prognosis of PDAC patients by inhibiting carcinogenesis, invasiveness, metastasis, and local recurrence. Therefore, a further, deeper understanding of the nerve-cancer interaction is needed for clinicians treating PDAC and their patients.

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