



Shedding Light on the Role of Neurotransmitters in the Microenvironment of Pancreatic Cancer

Yiyi Liang[†], Huimin Li[†], Yu Gan* and Hong Tu*

State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

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*Correspondence:

Yu Gan
ganyu@shsci.org
Hong Tu
tuhong@shsci.org

[†]These authors have contributed
equally to this work

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Pancreatic cancer (PC) is a highly lethal malignancy with a 5-year survival rate of less than 8%. The fate of PC is determined not only by the malignant behavior of the cancer cells, but also by the surrounding tumor microenvironment (TME), consisting of various cellular (cancer cells, immune cells, stromal cells, endothelial cells, and neurons) and non-cellular (cytokines, neurotransmitters, and extracellular matrix) components. The pancreatic TME has the unique characteristic of exhibiting increased neural density and altered microenvironmental concentration of neurotransmitters. The neurotransmitters, produced by both neuron and non-neuronal cells, can directly regulate the biological behavior of PC cells via binding to their corresponding receptors on tumor cells and activating the intracellular downstream signals. On the other hand, the neurotransmitters can also communicate with other cellular components such as the immune cells in the TME to promote cancer growth. In this review, we will summarize the pleiotropic effects of neurotransmitters on the initiation and progression of PC, and particularly discuss the emerging mechanisms of how neurotransmitters influence the innate and adaptive immune responses in the TME in an autocrine or paracrine manner. A better understanding of the interplay between neurotransmitters and the immune cells in the TME might facilitate the development of new effective therapies for PC.

Keywords: pancreatic cancer, tumor microenvironment (TME), neurotransmitter, immunotherapy, immune cells

INTRODUCTION

Although the accumulation of genetic and epigenetic defects is believed to drive carcinogenesis, the progression of cancer is indeed highly dependent on the interactions between cancerous and non-cancerous cells in the tumor microenvironment (TME). Immune cells make a large contribution to the non-malignant cellular components in the TME (Ho et al., 2020). Tumor-infiltrated immune cells bring out an important and complicated regulatory function in cancer progression. The TME also includes multiple secreted non-cellular components, such as cytokines, neurotransmitters and extracellular matrix (Dey et al., 2020; Winkler et al., 2020). Among them, neurotransmitters are recently emerging as a novel non-cellular portion of the TME that have been appreciated in cancer progression, especially in pancreatic cancer (PC) (Tan et al., 2021).

Pancreatic cancer is a devastating malignant disease with a very dismal prognosis (Ligorio et al., 2019). PC has a unique TME characterized by a markedly increased neural density. Neural remodeling and perineural invasion (PNI), the term describing the neoplastic invasion of tumor cells into nerves, are two common adverse histological characteristics of PC. As a group of chemical substances released by neurons, neurotransmitters have been documented to play a vital role in PC (Renz et al., 2018b). Altered concentration of several neurotransmitters is usually observed in the TME of PC and is associated with increased cancer aggressiveness and worsened overall prognosis (Biffi et al., 2019; Jurcak and Zheng, 2019; Hosein et al., 2020). PC cells showed chemotaxis toward neurotransmitters. Neurotransmitters can directly regulate the biological behavior of PC cells via binding to their corresponding receptors on tumor cells and activating the intracellular downstream signals (Entschladen et al., 2008). Moreover, recent studies have revealed that neurotransmitters do not only act on cancer cells, but also communicate with the immune cells in the TME (Binnewies et al., 2018), which suggests an indirect role of neurotransmitters in regulating the fate of PC by the crosstalk between neurotransmitters and the immune microenvironment in PC.

In this review, we will summarize the present progresses on the functions of neurotransmitters in the TME of pancreatic cancer. We will not only present the literatures that support direct effects of neurotransmitters on PC cells, but also discuss the interplay between neurotransmitters and the tumor immune microenvironment. Lastly, we will provide our perspectives on the potential therapeutic strategies the targeting neurotransmitter-immune cell crosstalk in PC.

NON-NEUROLOGICAL ROLES OF NEUROTRANSMITTERS IN CANCERS

Classification, Origin and Operation of Neurotransmitters

Neurotransmitters are biochemical molecules that carry information between neurons or between neurons and effector cells (Orrego, 1979). Most neurotransmitters are typically water-soluble molecules with dissociating groups. Based on their chemical structure, the critical classification of neurotransmitters can be summarized as follows (Spitzer, 2015): biogenic amines, amino acids, peptides, and other categories. Biogenic amine neurotransmitters are composed of dopamine (DA), norepinephrine (NE), epinephrine (E), and serotonin (5-HT). Amino acid neurotransmitters contain gamma-aminobutyric acid (GABA), glycine, glutamate, histamine, and acetylcholine (ACh). Peptide neurotransmitters include substance P (SP), neuropeptide Y (NPY), calcitonin gene related peptide (CGRP) and many others. Also, neurotransmitters can be classified by their function (excitatory or inhibitory) or by their action (direct or neuromodulator). Excitatory neurotransmitters (such as NE) activate the postsynaptic neuron and facilitate interneuronal information transduction, while inhibitory neurotransmitters (such as GABA) inhibit the postsynaptic neuron and hinder

information transduction. Some neurotransmitters can be both excitatory and inhibitory. Neuromodulators (such as 5-HT and DA) do not directly participate in interneuronal information transduction, but work together with excitatory or inhibitory neurotransmitters to modify the postsynaptic cell's response (Boto and Tomchik, 2019). Differ from neuromodulators in the extent of actions, neurohormones (such as oxytocin and vasopressin) are secreted by neurosecretory cells into the blood stream and exert their effect on distant peripheral targets (Iovino et al., 2019).

Emerging evidence demonstrates that neurotransmitters can be released not only by the neurons from the central or peripheral nervous system, but also by non-neuronal cells (**Table 1**). For instance, ACh, the first established neurotransmitter, has been found to be synthesized in a variety of non-neuronal cells such as epithelial cells (from airway, digestive tract, urogenital tract, or epidermis), mesothelial cells (from pleura or pericardium), endothelial cells, fat cells, and fibroblasts (Reijmen et al., 2018; Elyada et al., 2019). The primary and secondary lymphatic organs of the immune system can be innervated by nerves. The local neurotransmitter thus can act as an immunomodulatory messenger to regulate the interaction between peripheral nerves and the lymphocytes (Zhang et al., 2014; Blanchart et al., 2017; Sung et al., 2017; Hujber et al., 2018). This peripheral innervation has been reported to participate in the development of immune cells (Allen et al., 2020). Meanwhile, the immune cells can also produce specific neurotransmitters such as 5-HT (Chen et al., 2015) to regulate the immune cells function and remodel the surrounding microenvironment through autocrine and paracrine approaches (Briggs et al., 2016).

In the nervous system, neurotransmitters mediate interneuronal communication in synaptic transmission. Although whether nerve-to-non-neuronal cell synapses or synapse-like structures exist outside of the nervous system is not yet known, the nervous system can influence non-neuronal cells through changing circulating neurotransmitter levels (Monje et al., 2020). In the tumor microenvironment, neurotransmitters may be also secreted from non-neuronal cells and confer both paracrine and autocrine effects on cancer cells, as well as immune cells.

The Role of Neurotransmitters in Cancer

Similar to the process of neovascularization and lymphangiogenesis, the formation of new nerve endings in the tumor is called neurogenesis. Neurogenesis is one of the determinants in tumorigenesis and cancer development (Boilly et al., 2017). Neurotransmitters serve as a link between intratumoral nerves and tumor cells in the TME. Tumor cells express various neurotransmitter receptors. Neurotransmitters released from nerve fibers in the TME can directly act on tumor cells by binding to their specific neurotransmitter receptors (Hanoun et al., 2015; Renz et al., 2018a,b). Meanwhile, tumor cells can also produce endogenous neurotransmitters in response to diverse stimuli from the microenvironment. For example, various types of tumor cells have been revealed to produce GABA. The elevated intratumoral level of GABA has been

TABLE 1 | The origin of neurotransmitters.

Neurotransmitters	Non-neuronal secretion	References
Norepinephrine	Thymic cells	Roggero et al., 2011; McBurney-Lin et al., 2019
Serotonin	Enterochromaffin (EC) cells of the gastrointestinal tract, thymic epithelial cells, cancer cells, immune cells, platelet	Lifantseva et al., 2017; Spohn and Mawe, 2017
Dopamine	Gastrointestinal tract, thymic epithelial cells, immune cells	Lifantseva et al., 2016; Liu C. et al., 2021
GABA	Cancer cells, the endocrine cells of pancreatic islets	Soltani et al., 2011; Kim et al., 2015
Substance P	Enterochromaffin (EC) cells of the gastrointestinal tract, thymic epithelial cells	Heitz et al., 1976; Zaidi and Matthews, 2013
NPY	Cancer cells	Gotzsche and Woldbye, 2016
CGRP	Immune cells	Bracci-Laudiero et al., 2002; Messlinger, 2018
Acetylcholine	Epithelial cells, immune cells, cancer cells	Brenner and Sakmann, 1978; Kawashima and Fujii, 2004
Histamine	Mast cells	Haas et al., 2008; Misto et al., 2019
Glutamate	Endocrine cells of pancreatic islets	Cabrera et al., 2008

observed in PC as well as ovarian cancer and breast cancer (Zhang et al., 2014; Jiang et al., 2019).

Neurotransmitters can affect almost all aspects related to tumor development including cell proliferation, angiogenesis, and metastasis (Boilly et al., 2017). Peripheral 5-HT generates a mitotic effect on a variety of tumor and non-tumor cells such as fibroblasts, smooth muscle cells, osteoblasts, mesangial cells, and endothelial cells (Alpini et al., 2008; Moon et al., 2020). Many studies have shown a potential stimulatory effect of 5-HT on cancer cell proliferation, invasion, dissemination, and tumor angiogenesis (Herr et al., 2017). Abnormal glutamate signaling showed carcinogenic potential in glioma, melanoma, breast cancer, and prostate cancer (Ribeiro et al., 2017; Sung et al., 2017; Yu et al., 2017; Anastas and Shi, 2019). Substance P and SP/NK-1 system have also been involved in the development and progression of many cancers such as glioma, colon cancer, and lung cancer (Munoz et al., 2011; Covenas and Munoz, 2014). Elucidating their specific roles in tumor biology especially in the TME may open up new windows for the diagnosis and treatment of cancers.

NEUROTRANSMITTERS IN THE TME OF PANCREATIC CANCER

Nerves and Neurotransmitters Are Key Components of Pancreatic TME

The TME of pancreatic cancer is characterized by nutrient deficiency, connective tissue hyperplasia and high nerve distribution. Paracrine signals derived by cancer cell promote

nerve axonogenesis or neurogenesis in the TME. The infiltrated nerve fibers can control cancer initiation, growth and metastasis. Nerve fibers in the pancreatic TME include axons originating from the sympathetic, parasympathetic, enteropancreatic or hepatic plexus, afferent nerve fibers and newly developed nerve fibers. Neuron as presynaptic cell can secrete neurotransmitters such as E/NE, which act on specific receptors to regulate tumor proliferation and metastasis. In PC cells, sensory (Saloman et al., 2016; Sinha et al., 2017) and sympathetic nerves activate the growth of PC cells through the liberation of substance P and E/NE. On the contrary, parasympathetic nerves inhibit PC cell growth via ACh, leading to the inhibition of PI3K/AKT and EGFR/ERK in cancer cell (Renz et al., 2018b). This opposite impact of sympathetic and parasympathetic nerves suggests that the development of PC is regulated through a balance of neural innervation.

Neural remodeling and PNI are important pathological characteristics of PC (Guo et al., 2013). Neural remodeling is manifested as the increased size and density of infiltrated nerves in the pancreas. PNI is considered as one of the main routes for PC recurrence and metastasis after surgical resection since it presents a structural conduit for cell migration. Recent studies have illustrated that multiple types of cells in the TME of PC contribute to neural remodeling and PNI (Li et al., 2014). New nerve fibers in the TME act as a rich source of neurotransmitters and neurotrophic factors (Zahalka and Frenette, 2020), which substantially affects the malignant potential of tumor cells and the disease progression. For example, the classical neurotransmitters NE and 5-HT have been found to be significantly increased in PC tissues (Zhao et al., 2014; Jiang et al., 2017), and the altered levels of different neurotransmitters have been demonstrated to be associated with PC recurrence, metastasis, and survival (Guo et al., 2013), suggesting that microenvironmental neurotransmitters function as an essential non-cellular component that contributes to PC progression (Schuller et al., 2012).

Direct Effects of Neurotransmitters on Pancreatic Cancer

Neurotransmitters in the TME can be released by tumor-infiltrating fibers, cancer cells and non-cancerous cells such as immune cells and epithelial cells (Entschladen et al., 2008; Boilly et al., 2017). Neurotransmitters have numerous regulatory functions on PC cells, which we summarized in **Table 2**.

Epinephrine and Norepinephrine

The classical neurotransmitters E and NE have been found to give promotion to PC progression through multiple mechanisms. E and NE are stress molecules produced by the sympathetic nervous system and linked to PC growth via β -adrenergic signaling in both *in vitro* and *in vivo* studies (Renz et al., 2018b). Specifically, E indirectly enhanced β -AR-dependent neurotrophin secretion, which in turn increased NE levels and promoted PC growth (Zhao et al., 2014). The activation of β -AR can promote tumor growth and angiogenesis via VEGF and metalloproteinase MMP2/MMP9 signaling pathways (Thaker et al., 2006). NE also tended to promote

TABLE 2 | Summary of the studies on the role of neurotransmitters in pancreatic cancer.

Neurotransmitters	Receptor	Effect on pancreatic cancer cells	PC cells or animal models	References
Norepinephrine	α , β adrenergic receptors	Norepinephrine promotes proliferation, migration, invasion and inhibits apoptosis of pancreatic cancer cell	Panc-1, MIAPaCa-2, BxPC-3, AsPc-1, HPAC, SW1990 cells	Huang et al., 2012; Guo et al., 2013; Qian et al., 2018
Serotonin	5-HT receptors	5-HT increased proliferation and prevented apoptosis of PDAC cell lines	Kras/Trp53/Pdx1-Cre (KPC) mice, BxPC-3, HPAC, Panc-1, and SW1990 cells	Jiang et al., 2017
Dopamine	D1-like receptors D2-like receptors	The antagonists of DRD2, pimozide and haloperidol, inhibited the proliferation and migration of pancreatic cancer cells	BxPC-3, Panc-1, MIAPaCa-2, Capan-1, CFPAC-1 cells	Jandaghi et al., 2016
GABA	GABA _A , GABA _B	GABA stimulates pancreatic cancer growth through overexpressing GABAA receptor pi subunit	KLM-1, SUIT-2, KP-1N, PK-1, PK-45P, PK59, MIA PaCa-2, Panc-1 cells	Takehara et al., 2007
Substance P	NK-1 receptor	SP induces pancreatic cancer cell proliferation and invasion via NK-1 receptor and the high expression of NK-1 receptor was associated with poor prognosis in patients	CAPAN-1, ASPC-1, PA-TU 8902, BxPC-3, MIAPaCa-2 cells	Munoz and Covenas, 2014, 2015
NPY	Y1-4 receptors	Y2 is strongly overexpressed in pancreatic cancer and may modulate angiogenesis	LsL-Kras ^{G12D} , LsL-Trp53 ^{R172H} , Pdx1-Cre (KPC) mice	Zhou, 1993; Waldmann et al., 2018
CGRP	Calcitonin-like receptor (CLR). Receptor activity-modifying protein 1 (RAMP1). Receptor component protein (RCP)	CGRP stimulates the growth of PU-PAN-1 tumor cells, and CGRP receptor antagonist CGRP8-37 inhibited this effect	PU-PAN-1 cells	
Acetylcholine	nAChR, mAChR	Administration of a muscarinic agonist suppresses pancreatic cancer tumorigenesis	LSL-Kras ^{+/G12D} ; Pdx1-Cre (KC) and LSL-Kras ^{+/G12D} ; LSL-Trp53 ^{+/R172H} ; Pdx1-Cre (KPC) mice, Panc-1 cells	Renz et al., 2018b
Histamine	Histamine1-4 receptors	When bound to H1HR, histamine induces proliferation and metastasis of PANC-1 cells. Activation of H2HR in PANC-1 cells tends to have the opposite effect of H1HR activation.	Panc-1 cell	Francis et al., 2013
Glutamate	AMPA receptors. Kainite receptors. NMDA receptors.	Glutamate increases pancreatic cancer cell invasion and migration	Su86.86 cells, BxPC-3 cells	Herner et al., 2011

PC progression through β -AR/PKA/STAT3 signaling pathway (Coelho et al., 2017).

Serotonin

The neurotransmitter 5-HT, as well as its receptors, was found to be elevated in PC tissues (Jiang et al., 2017). Knockdown of 5-HT receptors inhibited the proliferation and invasion of human PC cells *in vitro* (Gurbuz et al., 2014). In contrast, the activation of 5-HT receptors enhanced glycolysis under metabolic stress, and thus promoted the growth of PC. Regarding its molecular mechanism, 5-HT stimulation increased the Warburg effect through PI3K-Akt-mTOR signaling (Jiang et al., 2017). In addition, the increased levels of type 1 tryptophan hydroxylase (TPH1), which was a key enzyme for peripheral 5-HT synthesis, and the decreased level of MAOA, which is responsible for 5-HT degradation, in PC tissues were correlated with the poor survival of patients (Jiang et al., 2017). Of importance, the metaplasia of acinar-to-ductal metaplasia (ADM) is a key determinant in PC development (Liou et al., 2017). Serotonin uptake by acinar cells could promote the activation of the small GTPase

Ras-related C3 botulinum toxin substrate 1 (Rac1), which is required for the transdifferentiation of acinar cells into ADM (Saponara et al., 2018).

Dopamine

The effect of DA on cancer cells is tumor type-specific. DA mainly reduced the proliferation and migration of endothelial cells in TME (Hoepfner et al., 2015). In PC, the dopamine receptor D2R is abnormally highly expressed and the antagonists of D2R (pimozide and haloperidol) were able to prevent the proliferation of PC cells, suggesting a PC-promoting effect of DA (Jandaghi et al., 2016).

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid is a major inhibitory neurotransmitter in the central nervous system (CNS). Different GABA receptors play different roles in tumor growth. GABA was found to enhance prostate cancer cell proliferation through the GABA-A receptor pathway (Blanchart et al., 2017) and to inhibit cancer cell growth through the GABA-B receptor pathway in

liver cancer (Wang et al., 2008; Hujber et al., 2018). GABRP, a subunit of the GABA-A receptor, was abnormally highly expressed in PC cells (Jiang et al., 2019). GABA treatment in GABRP-positive PC cells increased intracellular Ca^{2+} levels and activated the MAPK/Erk cascade, which led to a pro-tumor effect on PC (Takehara et al., 2007).

Neuropeptides

Neuropeptides, such as substance P, CGRP, and NPY, were also found to have a direct effect on PC cells. Substance P was a powerful regulator to PNI in PC during the early stage of primary tumor formation via the MMP1/PAR1/SP/NK-1R paracrine loop (Huang et al., 2018). Besides, substance P induced cancer cell proliferation and invasion as well as the expression of MMP-2 in PC cells, and sensory nerves in TME may help PC progression in part through up-regulation of its receptor (Sinha et al., 2017). Human PC cells possess distinct CGRP receptors. CGRP can stimulate the proliferation of human PC cells, suggesting a role of CGRP in the growth of PC cells (Zhou, 1993). What's more, CGRP and substance P derived from pancreatic stellate cells mediated the PC pain via activation of sHH signaling pathway (Han et al., 2016), which provided a novel therapeutic option for PC pain. NPY could be detected in both human and murine pancreatic samples. Its receptor Y2 was significantly increased in PanIN lesions and PC samples both in murine and human. The enhanced Y2 receptor-mediated NPY signaling may modulate the angiogenesis of PC (Waldmann et al., 2018).

Effects of Neurotransmitters on Non-malignant Cells in Pancreatic TME

In addition to affecting tumor cells, neurotransmitters can also improve angiogenesis, lymphangiogenesis, and inflammatory responses via exerting influence on endothelial cells and stromal cells in the TME. For instance, the activation of β -AR (β_2 and β_3) expressed on stromal cells promotes the survival of prostate cancer cells via TGF- β signaling (Magnon et al., 2013). Neovascularization is a vital process involved in tumor growth and metastasis. There is substantial evidence indicating that vascular endothelium infiltrated in the TME expresses various neurotransmitter receptors such as E and NE (Sarkar et al., 2013). NE could also stimulate endothelial cell metabolism and drive angiogenesis in tumors (Zahalka et al., 2017; Hondermarck and Jobling, 2018). DA was shown to mobilize endothelial progenitor cells from the bone marrow and participate in angiogenesis in the TME (Chakroborty et al., 2008). Neuropeptide Y released by tumor cells interacts with receptors on endothelial cells or immune cells, modulating tumor-related angiogenesis and local inflammatory responses (Medeiros and Jackson, 2013). Meanwhile, neurotransmitters can also regulate stromal cells in the microenvironment. Using a high-throughput drug screening system that focuses on the pancreatic stellate cells, Sagara et al. found that dopamine antagonist could inhibit the activation of pancreatic stellate cells and suppressed the invasion of pancreatic cancer cells by disrupting tumor-stromal interaction (Sagara et al., 2021). In addition, 5-HT was demonstrated to be essential for the survival and activation of hepatic stellate cells. Serotonin-activated stellate cells could promote carcinogenesis

and contribute to sex disparity in hepatic cell carcinoma (Yang et al., 2017).

INTERPLAYS BETWEEN NEUROTRANSMITTERS AND THE IMMUNE CELLS IN PANCREATIC TME

Immune Cells in the TME of Pancreatic Cancer

Intratumoral immune heterogeneity is considered as a hallmark feature of the TME (Riggin et al., 2021). The tumor immune microenvironment has an immense influence on tumor initiation, progression and therapeutic response. Immune effector cells such as CD8^+ cytotoxic T cells (CTL) and natural killer (NK) cells infiltrated in the TME keep the malignant cells under surveillance and form “barriers” to restrain cancer cell metastasis (Kurtulus et al., 2019). The secretion of multiple cytokines in pancreatic TME effect T helper (TH) cells, especially switching the balance of TH1/TH2, and contribute to the immunosuppressive microenvironment (Ho et al., 2020). Dendritic cells (DCs) are also considered as a significant component in adaptive anti-tumor immunity. DCs get involved in the proliferation of CTL in the TME (Puleo et al., 2018; Binnewies et al., 2019; Wculek et al., 2020) due to their role in tumor antigen recognition and presentation that stimulates T cell activation.

On the other hand, the TME can provide an immunosuppressive niche to negatively regulate immune effector cells and facilitate the malignant progression of cancer (Ho et al., 2020), and causes the resistance of PC against various treatments such as chemotherapy, targeted therapy, and immunotherapy (Balachandran et al., 2019). The major immunosuppressive cell types in the TME of pancreatic cancer are tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Treg), TH17, and tolerogenic DCs (Bronte and Tortora, 2016; Zhu et al., 2017; Ligorio et al., 2019; Zhang et al., 2020). These immunosuppressive cells promote tumor progression through a variety of mechanisms, including the direct mediation, inhibition of tumor-killing immune cells, induction of angiogenesis and lymphoangiogenesis (Ho et al., 2020), and promotion of metastasis. TAMs and MDSCs predominate in the TME and continuously communicate with PC cells to propagate disease progression (Lin et al., 2019). TAMs foster immune escape in the TME by suppressing TH1 cell and the antitumor responses of CTL. These contribute to matrix remodeling and facilitate tumor cell migration and invasion and promote tumor angiogenesis and growth (Qian and Pollard, 2010; Binnewies et al., 2018; Halbrook et al., 2019). MDSCs are known to exert immunosuppressive effects on T cells via secreting arginase, nitric oxide synthase, TGF- β , IL-10, and COX2 (Zhang et al., 2017). Tregs suppress tumor immunity in PC through a variety of pathways including the secretion of IL-10, TGF- β , and granzyme B, the activation of the TRAIL pathway and enhancement of T cells' dysfunction (Zhang et al., 2020). TH17 cells are able to promote tumor cell

growth by secreting IL-17, IL-23, and CCL20 (Wu H.H. et al., 2015), and inhibit the CD8⁺ T-mediated immune response by IL-17 and IL-22 (Yan and Richmond, 2020). Tumor-infiltrating lymphocytic B cells (TIL-B) resident in tertiary lymphoid structures were associated with better survival in PC patients, while TIL-B got involved in the initiation and progression of PC (Roghianian et al., 2016; Wouters and Nelson, 2018; Mirlekar et al., 2020).

As more TAMs were found in PC with PNI compared to that without PNI (Li et al., 2014; Alrawashdeh et al., 2019), the infiltration of immunosuppressive cells has been considered to relate to the PNI, which is the prominent characteristic of PC. Being the key molecular mediators of neuroimmune interactions, neurotransmitters might mediate the PNI-induced infiltration of immunosuppressive cells in PC. The PNI of pancreatic cancer could mediate β -AR signaling, and the released Ach enhanced tumor growth by establishing an immune-suppressive TME characterized by impaired CTL infiltration and a reduced TH1/TH2 ratio (Yang et al., 2020).

Immune Cells as Non-neuronal Sources of Neurotransmitters

In recent years, promising studies have drawn the attention that immune cells in different activated states can synthesize or store neurotransmitters participate in neuroimmune regulatory circuits (Marino and Cosentino, 2013). Immune cells such as activated TH cells, Treg cells, and mature DC are able to synthesize or release serious classical neurotransmitters and their metabolites, including Ach, DA, and 5-HT. The synthesis of Ach was firstly observed in T cells (Ogawa et al., 2003). Compared with CD8⁺ T cells or B cells, CD4⁺ T cells contain more Ach (Kawashima and Fujii, 2003). TH cells could express tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of DA, and store DA in the intracellular vesicles (Cosentino et al., 2000, 2007; Nakano et al., 2009). The inhibitory neurotransmitter such as 5-HT could be secreted by T cells, DCs, and macrophages (O'Connell et al., 2006; Wu et al., 2017).

Of interest, immune cells such as activated T cells have the capacity to synthesize 5-HT, and this potential is enhanced during their activation (O'Connell et al., 2006; Chen et al., 2015). CD8⁺ T cells were found to selectively express the highest level of type 1 tryptophan hydroxylase (TPH1), an enzyme that catalyzes the conversion of L-tryptophan (a direct precursor of 5-HT), indicating that they are capable of producing 5-HT. DCs and B cells can accumulate 5-HT through a regulated uptake mechanism from the microenvironment or activated T cells via serotonin transporters (SERTs) (Chen et al., 2015). Specifically, the expression of SERT on the surface of DC cells would increase as DCs matured or activated (Katoh et al., 2006), and also dynamically adjusted with the change level of 5-HT in the microenvironment (Arreola et al., 2015). Once DCs contact with T cells, their SERT expressions would significantly up-regulate (Chen et al., 2015). The stored 5-HT in DCs within LAMP-1⁺ vesicles were subsequently released via Ca²⁺-dependent exocytosis. Thus, DCs could sequester 5-HT, which are released from the microenvironment or directly from

activated T cells, and transmit this 5-HT to naive T cells. This process suppressed cAMP production and thereby facilitated the activation and differentiation of naive T cells (O'Connell et al., 2006; Sacramento et al., 2018).

The Regulatory Effect of Neurotransmitters on Immune Cells Infiltrated in the Pancreatic TME

Neuro-immune interactions rely on soluble signaling molecules between cells, which including cytokines, chemokines, neurotransmitters, and neurotrophins. Neurotransmitters can regulate both the local and systemic immune responses against cancers. There is a comprehensive neuro-immune regulatory network existing in the TME, and the communication between neurotransmitters and immune cells influences the fate of cancer with either promoting or inhibiting the cancer growth and metastasis. The well-studied immune mediations caused by neurotransmitters are summarized in **Table 3** and **Figure 1**. Understanding the regulatory effects of various neurotransmitters on cancer immunity can help to design new strategies for cancer therapy.

Epinephrine and Norepinephrine

E and NE are mainly secreted by the adrenal medulla and sympathetic nerves, respectively. Local sympathetic innervation provides the bulk of the catecholamine content within the tumor (Zahalka and Frenette, 2020). Excessive activation of sympathetic nerves could damage the anti-tumor immune response, increase the invasion ability of tumor cells, and accelerate the occurrence and development of tumors (Nissen et al., 2018).

E and NE mainly exert immunosuppressive effects. The receptor β -ARs is present in most immune cells such as T cells (including Treg), B cells, macrophages, NK and DC cells (Sarkar et al., 2013). E and NE can inhibit the activity of CD8⁺ T and NK cells via inducing the apoptosis of these lymphocytes (Zhao et al., 2014). They are known to directly suppress the production of cytokines and T cell proliferation, and potentially inhibit TCR-mediated integrin activation on human antigen-specific CD8⁺ T cells (Leone et al., 2015; Dimitrov et al., 2019). β -AR signal suppressed the production of IL-2 and IFN- γ and proliferation of CD4⁺ T cells depending on their stage of differentiation (Muthu et al., 2007). The combined application of endogenous E and prostaglandin could reduce the anti-tumor activity of NK cells, thereby promoting the progression of leukemia (Inbar et al., 2011; Meron et al., 2013). Besides, several studies have demonstrated that chronic adrenergic signaling suppresses NK cell activity in solid tumors (Melamed et al., 2005; Tarr et al., 2012; Graff et al., 2018). In addition, β -AR-mediated hormonal signaling could reduce the deformability of macrophages, resulting in the acceleration of tumor metastasis (Kim et al., 2019). NE and E contribute to the macrophage polarization, recruitment, and cytokine production like IL-6 and TNF- α (Izeboud et al., 1999; Chiarella et al., 2014). Activation of β -AR signal could increase the infiltration of macrophages in the primary tumor parenchyma and induce the M2 polarization of macrophages (Dimitrov et al., 2019), which subsequently promoted tumor metastasis and

TABLE 3 | Summary of the functions of neurotransmitters on immune cells.

Neurotransmitters	Immune cells	Effect	References
Epinephrine, norepinephrine	T-lymphocytes	Inhibit the activity of CD8 ⁺ T cells	Inbar et al., 2011; Dimitrov et al., 2019; Kim et al., 2019
	NK cells Macrophages	Inhibit the activity of NK cells Activation of β -AR signal could increase the infiltration of macrophages in the primary tumor parenchyma and induce the M2 polarization of macrophage, which subsequently promoted tumor metastasis	
Serotonin	T-lymphocytes	Releases IL-2, 16 and IFN- γ , T-cell proliferation	Uyttenhove et al., 2003; Yin et al., 2006; Mikulski et al., 2010; Inoue et al., 2011
	Dendritic cells	Increasing the Ca ²⁺ concentration in immature cells Activating 5-HT ₄ and 5-HT ₇ promotes the differentiation and maturation of DCs, up-regulates intracellular cAMP levels, and promotes the secretion of cytokines, such as IL-1 β , IL-6, IL-8, and IL-10	
	Macrophages	Down-regulating chemokine CCR5 expression and up-regulating chemokine CCL2 and MIP1 α expressions. Activating 5-HT ₂ increases the production and release of M2 cytokines. Inhibits release of TNF- α , inhibits NK cell suppression.	
Dopamine	Neutrophils	Inhibits tumor cell phagocytosis and oxidative burst	Sarkar et al., 2006, 2013; Levite, 2016; Talhada et al., 2018
	T-lymphocytes	T cells express functional dopamine receptors (DR) D1R-D5R, but their level and function are dynamic and context-sensitive; DA affects Th1/Th2/Th17 differentiation; D2 activation induces T cells to secrete IL-10; D3 activation promotes T cells to secrete TNF- α , IFN- γ D5 activation promotes T cells to secrete TNF- α and IL-10 Activation of D1 and D4 up-regulate the activity of cAMP and transcription factors STAT5 and GATA3, and promote the differentiation of T cells to TH2 DA inhibits the suppressive activity of Treg DA activates resting effector T cells (Teffs) resulting in their proliferation and cytokine production. T cells produce DA (Tregs >>> Teffs), release DA, mainly after mitogen/antigen/CD3 \pm CD28/PKC activation, uptake extracellular dopamine, and need DA. DA is important for antigen-specific interactions between T cells and dendritic cells.	
	Dendritic cells	Activating the D1 receptor on DC promotes ERK/JNK/NF- κ B signaling, and inducing cytokine production	
	B-lymphocytes	Activating the D1 receptor on B cells increases the expression of its inducible ICOSL and CD40L	
GABA	T-lymphocytes	Suppressing the immune effect by inhibiting the activation of NF- κ B.	Bergeret et al., 1998; Prud'homme et al., 2015
	Macrophages	Inhibiting the activation of macrophages by blocking calcium signals. Up-regulating the expression of the chemokines CXCL5 and CCL20.	
Substance P	T-lymphocytes	Affecting the activity and migration ability of CD8 ⁺ T cells	Mashaghi et al., 2016; Shahzad et al., 2018
	Dendritic cells	Regulating the movement of dendritic cells toward lymph nodes via modulating the expression of chemokine receptors and adhesion molecules.	
	Macrophages	Activating NF- κ B signaling in macrophages increases the production of pro-inflammatory cytokines, and therefore amplified the inflammatory response mediated by Th1 or Th17	
	Peripheral blood monocytes	Producing pro-inflammatory cytokines, such as IL-1, IL-6, IL-12 and TNF- α	
NPY	Neutrophils	Participating in migration of neutrophils	Wheway et al., 2007a,b
	T-lymphocytes	Promoting the polarization of Th2 polarizing by upregulating the production of IL-6 and IL-10	
CGRP	Dendritic cells	Inducing migration of immature DCs through the engagement of NPY Y1 receptor and the activation of ERK and p38, and exerting proinflammatory effects through the recruitment of immature DCs	Fox et al., 1997; Holzmans, 2013
	Macrophages	Inhibition macrophages and upregulation of IL-10, IL-10-independent induction of the inducible cAMP early repressor (ICER) and inhibition of NF- κ B activity	

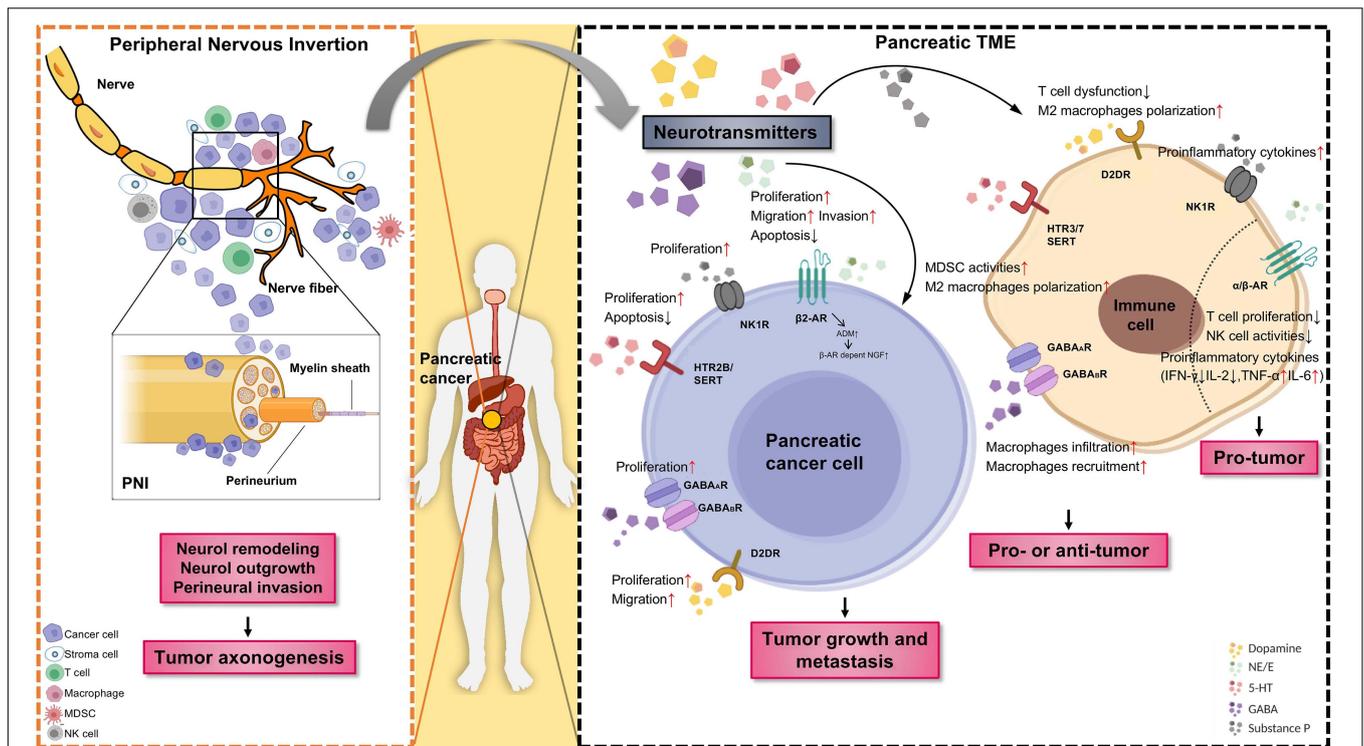


FIGURE 1 | The role of neurotransmitters and the emergence of nerves in the pancreatic tumor microenvironment (TME). Tumor innervation is present as shown by the extension of nerve fibers into the solid tumor, while perineural invasion (PNI) is present as shown by the invasion of cancer cells into the perineurium of the nerve (**Left panel**). The outgrowth of nerves in TME (axonogenesis) is partly driven by the secretion of neurotransmitters released by sympathetic nerves and other tissues or cells. In return, nerve fibers as branches of neuron infiltrate the TME, could regulate tumor growth and metastasis. Schematic representation of different neurotransmitters, their respective receptors, target cells as well as pro/antitumor activity of specific neurotransmitter/receptor axis (**Right panel**). Neurotransmitters are an active component of the TME. Neurotransmitters released by neuro-endocrine-immune system and other tissues or cells can promote cancer cell proliferation, migration, and invasion through the stimulation of specific membrane receptors. Moreover, immune cells infiltrated in the TME likewise express diverse neurotransmitter receptors and react with neurotransmitter, are known to have a strong impact on tumor angiogenesis and inflammation. PNI, perineural invasion; TME, tumor microenvironment; MDSC, myeloid-derived suppressor cells. The figure was created with BioRender.com.

stimulated tumor cells to produce chemokines like M-CSF (Van Overmeire et al., 2016). The use of β -blocker propranolol reduced the immunosuppression function of MDSC in breast cancer and enhances the effect of other cancer therapies like anti-PD-1 treatment and irradiation (Mohammadpour et al., 2019).

In pancreatic TME, it was shown that NE and E could decrease the expressions of MHC-I molecules and the costimulatory ligand B7-1 in PC cells, and increase the expressions of immunosuppressive IDO, PD-1, and PD-L1 (Arreola et al., 2015). Although these changes only last for a short time, these phenotypic changes of cancer cells do not only prevent the antigen recognition by T cells, but also damage T cell function by depleting essential nutrients, such as tryptophan, and inducing the exhaustion of activated lymphocytes (Zhao et al., 2014). β -adrenergic activation directly inhibits the generation of CTL and blocks the recruitment of protective T cells in the tumor microenvironment (Nakai et al., 2014). In PC, stress-induced neural activation is related to increased primary tumor growth and tumor cell dissemination to the normal adjacent pancreas. These effects were associated with increased expression of invasion genes by tumor cells and pancreatic stromal cells in the microenvironment (Kim-Fuchs et al., 2014). Enriching

the housing environment for mice could enhance the cytotoxic activity of NK cells and promote tumor-infiltrating NK cells via sympathetic nerve-dependent mechanisms. Application of the β -blocker largely abolished the effects of the enriched environment on NK cells and attenuated its anti-tumor function (Song et al., 2017).

Taken together, adrenergic signaling mainly exhibits pro-tumorigenic properties. This effect is generated in part through the enhanced immune evasion induced by E and NE. The inhibition of adrenergic signaling increases the antitumor immune response via its impact on multiple immune cells, supporting the potential value of adrenergic antagonists in cancer prevention and treatment.

Serotonin

In the brain, 5-HT is synthesized by neurons located in the raphe nucleus of the brainstem (Migliarini et al., 2013). Externally, less than 1% of free 5-HT exists in the blood, and the rest is stored in platelets, presynaptic neurons, and intestinal enterochromaffin cells (Kim et al., 2019). 5-HT is a multifunctional molecule that regulates immune function (Arreola et al., 2015). It is now known

that there are seven different 5-HT receptor subtypes: 5-HT1 to 5-HT7. Except 5-HT3, which is a ligand-gated ion channel, all the other 5-HT receptors belong to the G protein coupled receptor family. Most immune cells express 5-HT receptors. 5-HT1 is mainly expressed in innate immune cells such as the mast cells (Kushnir-Sukhov et al., 2006), macrophages (Nakamura et al., 2008), DCs (Durk et al., 2005), and monocytes (Soga et al., 2007); 5HT-2 is expressed in eosinophils and macrophages (Mikulski et al., 2010). In the adaptive immune system, proliferated T cells mainly express 5-HT1B, 5-HT2A, and 5-HT7, and B cells mainly express 5-HT1A and 5-HT3 (Yin et al., 2006; Inoue et al., 2011).

5-HT is a neuromodulator with neurotransmitter and neuroendocrine functions in cancer (Balakrishna et al., 2021). Meanwhile, it also regulates a variety of immune processes, such as immune cell chemotaxis, activation, proliferation, and cytokine secretion (Herr et al., 2017). SERT blockers including the serotonin selective reuptake inhibitors (SSRI) which increase extracellular 5-HT concentration have immunoinhibitory effects (Gobin et al., 2014). In T cells, 5-HT induces T cell differentiation into Treg cells and promotes the shift of Th17 cells to Tregs. 5-HT acts on Th17 to induce the secretion of IFN- γ and IL-17 and elevates the release of IL-10 from Tregs, which indirectly promote the development of tumors (Sacramento et al., 2018). In DC cells, 5-HT elevates the Ca²⁺ concentration in immature cells, and contributes to the differentiation and maturation of DCs by activating 5-HT4 and 5-HT7. This activation could up-regulate cAMP levels in DCs (Carhart-Harris and Nutt, 2017) and the secretion of related cytokines such as IL-1 β , IL-6, IL-8, and IL-10 (Idzko et al., 2004; Katoh et al., 2006). In macrophages, 5-HT regulates the polarization of macrophages through both activated and inhibitory signals. 5-HT2A activation increases the production of M2-type cytokines and migration while 5-HT1A activation enhances the capability of phagocytosis in macrophages (Mikulski et al., 2010; de las Casas-Engel et al., 2013). Activation of 5-HT1A on lung cancer cells could induce immune evasion via autophagy. After the activation, the ratio of TH1/TH2 cells decreased and the number of Tregs increased in TME, which suggesting a resistance to CTL attack (Liu et al., 2019).

In the pancreas, 5-HT is profoundly implicated in acute pancreatitis, pancreas regeneration after pancreatitis and PC. In the pancreatic TME, the SSRI fluoxetine reduced the stromal reaction that surrounds pancreatic lesions, evidenced by decreased fibrosis, inflammation and angiogenesis (Saponara et al., 2018). The intratumoral MAOA expression was also associated with T cell dysfunction and decreased patient survival in a broad range of cancer patients including PC (Wang et al., 2021).

In summary, in most cases, serotonin signaling influences immune cells and facilitates tumor development via suppression of anti-tumor immunity. Therefore, the use of anti-anxiety or anti-depressant drugs targeting serotonergic system may have potential implications in cancer therapy.

Dopamine

Dopamine contributes to neuroimmune communication and acts on immune cells in an autocrine/paracrine manner through its

receptors (Roy et al., 2000). Dopamine receptors are functionally classified into the D1-like subtypes consisting of D1R and D5R and D2-like subtypes (D2R, D3R, and D4R receptors), based on their ability to stimulate the formation or inhibition of cAMP (Kebabian, 1978).

Dopamine mainly acts on T cells and trigger DA receptor-dependent activation of ERK, LCK, FYN, and NF- κ B pathways (Ghosh et al., 2003). In T cells, the activation of D2R and D5R can induce IL-10 (Besser et al., 2005; Cosentino et al., 2007), while D3R activation induces TNF- α and IFN- γ secretion (Ilani et al., 2004). Besides, the stimulation of D3R in naive CD8⁺ T cells also contributed to the regulation of chemotaxis and related cellular function like extravasation and adhesion (Huang et al., 2010; Figueroa et al., 2017). DA affects Th1/Th2/Th17 differentiation. Specifically, the activation of D1R and D4R enhanced the TH2 differentiation by up-regulating the activity of cAMP, STAT5, and GATA3. Besides, DA mediated the chemotactic migration of naive CD8⁺ T cells by inducing chemokines like CCL19, CCL21, and CXCL12 (Watanabe et al., 2006). It was reported that DA inhibits the proliferation of T cell and the secretion of IL-2, IL-6, and IFN- γ when exposed to a high level of DA (Bergquist et al., 1997; Saha et al., 2001). DA could activate D1-like receptors in Treg, which in turn indirectly activates effect T cell (Cosentino et al., 2007). Except for T cells, inhibition of the DR3-mediated signal in DC cells increased the cross-presentation of antigen to CD8⁺ T cells (Figueroa et al., 2017).

Dopamine functions as a regulatory component on immune cells in the TME (Yan et al., 2015; Petrilli, 2017). Increased level of plasma DA (40–80 pg/ml) was reported to evidently impair physiological proliferation and cytotoxicity of T cells in cancer patients (Saha et al., 2001). In PC, DA enhanced the chemotherapeutic efficacy of gemcitabine both *in vitro* and in immunocompetent murine models, and changed TME by suppressing the M2 characters of TAMs. Specifically, the activation of D4R in macrophages by DA reduced the production of cAMP, and then inhibited the activation of PKA/p38 signal pathway, which suppressed the transcription of tumor-promoting cytokines of TAMs such as IL-1 β and TNF- α (Liu Q. et al., 2021). What's more, DA was found to hinder the function of tumor-induced monocytic MDSCs on the proliferation and IFN- γ production of T cells in lung and melanoma cancer (Hoeppner et al., 2015; Wu J. et al., 2015). DA attenuated NO production by MDSCs directly, mediated by decreased iNOS expression and the downregulation of ERK and JNK signaling pathways. DA-induced activation of resting Tregs and suppression of Tregs seem beneficial for the immunotherapy of cancer. As for the receptors, D2R was identified as an upregulated protein in PC, and D2R antagonists (pimozide and haloperidol) reduced PC growth and particularly metastasis (Jandaghi et al., 2016). The anti-tumor efficacy of ONC201 and ONC212, two small molecule antagonists of D2R, were observed *in vivo* either administrated as a single agent or in combination with 5-fluorouracil, irinotecan, and oxaliplatin. When treated with ONC201, a broad induction of immune cytokines and effector molecules was observed among PC patients with longer progression-free survival (Lev et al., 2017; Stein et al., 2019). Besides, ONC201 has been reported to induce the proliferation of

NK cells and activation via TRAIL and granzyme B in preclinical studies (Stein et al., 2019).

Together, the current findings suggest an important immunomodulatory effect of DA in cancer microenvironment. DA may confer immunopromoting or immunosuppressive effect dependent on the types of immune cells and the specific DA receptor they express.

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid is the main inhibitory neurotransmitter in the central nervous system. In the periphery, GABA is produced by pancreatic β cells, T cells, and macrophages. These cells also express other components of the GABAergic system, including receptors, transporters, and metabolic enzymes (Wu et al., 2017). The GABAergic signaling system affects various functional characteristics of immune cells, such as antigen-induced T cell proliferation (Bjurstom et al., 2008) and LPS-induced cytokine release and effector T cell activity (Lang et al., 2003).

Both *in vivo* and *in vitro* studies have proved that GABA suppresses the immune effect by inhibiting the activation of NF- κ B and reducing the production of inflammatory cytokines (Bhat et al., 2010). As a negative regulator in the TME, GABA inhibits the activation of macrophages and T cells by blocking calcium signals and inhibiting NF- κ B pathway (Prud'homme et al., 2015). In addition, GABA was shown to regulate the expression of GABA-A receptor subunits on immune cells (Bergeret et al., 1998; Feske et al., 2012). In the pancreatic TME, GABRP expression was remarkably increased in PC tissues among other neurotransmitters' receptors. GABRP expression correlated with macrophages density closely, and the deletion of macrophages largely abrogated the oncogenic functions of GABRP in PC. The GABRP on cancer cells promoted macrophages recruitment by inducing CXCL5 and CCL20 expression. Specifically, GABRP might act as a chaperone protein and regulate the activity of KCNN4 channel to induce Ca^{2+} signaling in PC cells. The GABRP-KCNN4 complex led to the activation of NF- κ B, which further facilitated CXCL5 and CCL20 transcription to induce macrophage infiltration in PC (Jiang et al., 2019).

In general, GABA exerts immunosuppressive effects on diverse immune cells and blockade of GABA signaling in the microenvironment may improve the anti-tumor immune response against cancer cells.

Neuropeptides

Most studies related to the immunomodulatory effect of neuropeptides focused on the substance P. In the central system, substance P is released from the brain regions and regulates emotions and specific sensory nerve endings (Cunin et al., 2011; Munoz and Covenas, 2015). In the periphery, substance P is mainly secreted by immune cells such as macrophages and DC cells (Janelsins et al., 2013). Substance P exerts its biological activity through G protein-coupled neurokinin receptors (NKRs), namely NK-1R, NK-2R, and NK-3R (Suvas, 2017). NK-1R mainly exists in the immune system and mediates the effect of substance P on immune cells (Shahzad et al., 2018).

Substance P acts on NK-1R to induce a local inflammatory environment in a concentration-dependent manner. Specifically, substance P mediates the migration, proliferation, and activation of immune cells. Substance P activated NF- κ B signaling in macrophages, increased the production of pro-inflammatory cytokines such as CCL2, CXCL2, and IL-8 (Levite, 2008). Therefore substance P amplified the inflammatory response mediated by TH1 or TH17 (Cunin et al., 2011; Mashaghi et al., 2016). Recent studies illustrated that administration of substance P during the primary immune response amplifies the secondary immune response by activating CD8⁺ T cells (Ikeda et al., 2007). Substance P increased the migration of immune cells, including T cells and neutrophils, through a β -arrestin-dependent mechanism (Nichols et al., 2012). Substance P also stimulated human PBMC to produce pro-inflammatory cytokines including IL-1, IL-6, IL-12, and TNF- α (Cunin et al., 2011). As for innate immune cells, substance P activated NK cells and neutrophils by up-regulating their production of cytotoxic-associated molecules, such as perforin and granzyme (Fu et al., 2011; Mashaghi et al., 2016). However, the up-regulation of the NK-1R can be seen in both chronic pancreatitis and PC and enhanced NK-1R expressions were related to advanced tumor stage and a poorer prognosis (Li et al., 2013). In addition, CD10⁺ fibroblasts can inhibit squamous cancer cells invasion ability by diminishing substance P (Xie et al., 2010).

The peripheral sensory nerves, which mediate pain reflexes, may influence immune responses through the release of neuropeptides CGRP (Holzmann, 2013). CGRP directly acts on macrophages and dendritic cells and inhibits the capacity of these cells to produce inflammatory cytokines and to present antigens to T cells. The molecular mechanisms, by which CGRP acts on innate immune cells, include the upregulation of IL-10, IL-10-independent induction of the inducible cAMP early repressor (ICER) and inhibition of NF- κ B activity (Fox et al., 1997). In addition, Liu et al. demonstrated that increased CGRP and neuronal p75 immune-reactivities in tumor-bearing mice, promoting chronic pain in bone metastasis (Liu et al., 2020).

Neuropeptide Y was found to induce a dose-dependent migration of immature DCs through the engagement of NPY Y1 receptor and the activation of ERK and p38. Meanwhile, NPY promoted the polarization of TH2 polarizing by upregulating the production of IL-6 and IL-10 (Wheway et al., 2007a,b). Thus, NPY may exert proinflammatory effects through the recruitment of immature DCs, but it may exert anti-inflammatory effects by promoting a TH2 polarization. In prostate cancer, depression-induced NPY secretion might promote the tumor infiltration of myeloid cells and therefore contribute to cancer progression (Cheng et al., 2019).

Taken together, the neuropeptides CGRP and NPY were suggested to impair the anti-tumor immunity and their inhibition may be a potential strategy for cancer treatment. On the contrary, substance P may facilitate the anti-tumor immune response. However, enhancing the substance P signaling in cancer cells could promote the progression of pancreatic cancer. The distinction between signaling mechanisms of

substance P in immune cells and cancer cells warrants further studies.

NEUROTRANSMITTER-TARGETED DRUGS AS COMBINATORIAL STRATEGIES FOR CANCER IMMUNOTHERAPY

The important role of neurotransmitters in cancer progression suggests that the drugs targeting neurotransmitter signaling may act as promising candidates for cancer treatment (Cole et al., 2015). In fact, the clinical trials of various neurotransmitter receptor antagonists or agonists are already ongoing (Table 4). Among them, β -blockers, which are the antagonists targeting adrenergic β receptors, are mostly studied (Botteri et al., 2013; Grytli et al., 2013a,b). Data from prostate cancer and breast cancer studies showed that patients using β -blockers, even former users, had significantly better survival outcomes than the non-users (Grytli et al., 2013b; De Giorgi et al., 2018). In melanoma, pan β -blockers provided more survival benefits

than β 1- or β 2-selective blockers (Livingstone et al., 2013). In PC, long-term use of beta-blockers especially selective β 1-blockers may be associated with decreased cancer risk (Saad et al., 2020). Besides, β -blocker drugs may lead to a significantly improved overall prognosis in PC patients, particularly among those with localized disease (Saad et al., 2020). These findings raise the possibility that neurotransmitters-related drugs protect from cancer initiation.

Recently, immunotherapy is emerging as the most promising treatment option for cancers. However, immunosuppressive mechanisms within the TME largely limit its therapeutic efficacy. As aforementioned, neurotransmitters not only have direct effects on tumor cells, but also contribute to the immunosuppressive microenvironment by acting on immune cells in the TME. Therefore, neurotransmitter-targeted drugs have attracted increasing attentions as a combinatorial approach for cancer immunotherapy. In murine tumor models, reducing β -AR signaling was shown to facilitate the conversion of TME to an immunologically active microenvironment, and β -blockers application significantly increased the efficacy of anti-PD-1 checkpoint blockade (De Giorgi et al., 2018). In addition, blocking β -AR signaling also improved the potency

TABLE 4 | Clinical trials related to neurotransmitters in cancer.

Related neurotransmitter	Cancer type and stage	Purpose	Strategy or treatment	Enrolled patients	Therapeutic effects	References
Catecholamine (E/NE)	Head and neck. Esophagus. Stomach. Colon. Prostate cancer.	Investigate the association between propranolol and cancer	Patients with a usage of propranolol > 6 months in NHIRD database	24,238	HR:0.58 (95%CI: 0.35–0.95) HR:0.35 (95%CI: 0.13–0.96) HR:0.54 (95%CI: 0.30–0.98) HR:0.52 (95%CI: 0.33–0.83) Reduce cancer risk	Chang et al., 2015
Catecholamine (E/NE)	Locally advanced and metastatic melanoma	Investigate the efficacy of combination with propranolol and pembrolizumab	Propranolol twice a day with pembrolizumab 200 mg every 3 weeks	9	In progress (ORR = 78%) Responders show increased IFN- γ and decreased IL6 level	Gandhi et al., 2021
Serotonin	Breast cancer with obesity or/and overweight	Exam the effects of Mediterranean Diet and Naltrexone/Bupropion Treatment in Obese Breast Cancer Patients	Naltrexone/bupropion combination (NB) ⁺ release (ER)	72	The combination of the Mediterranean diet with naltrexone/bupropion treatment Without superior changes	NCT03581630 (Cho et al., 2020)
Dopamine	Pituitary adenoma; Non-functioning pituitary adenoma	Investigate the efficacy of cabergoline in NFPA individuals with remaining tumor after primary neurosurgery	Cabergoline (a DRD2 antagonist and antiparkinson drug)	140	Residual tumor shrinkage: 10.5% vs. 28.8%, stabilization = 66.1% vs. 73.7%, enlargement = 5.1% vs. 15.8% (the control group) PFS: 23.2M vs. 20.8M (the control group)	NCT03271918 (Batista et al., 2019)
Dopamine	Recurrent and stage IV breast cancer	Investigate the effectiveness of cabergoline in treating metastatic breast cancer disease in those who test positive for the prolactin receptor	Cabergoline (a DRD2 antagonist and antiparkinson drug)	20	CBR = 33% (6/18), mPFS = 1.8M, mOS = 10.4M	NCT01730729 (Costa et al., 2017)
Dopamine	Advanced solid cancer refractory to the standard treatment	Evaluate the safety and pharmacokinetics of weekly ONC201	ONC201 (a DRD2 antagonist)	20	Enhance immunostimulatory activity	NCT02250781 (Stein et al., 2019)

of TCR- γ T-cell therapeutics in hematologic malignancies (Baker et al., 2019) and enhanced the antitumor efficacy of STxBE7-based cancer vaccine in a breast cancer model (Daher et al., 2019). Small-molecule MAO inhibitors (MAOIs), used for depression and other neurological disorders, was found to significantly suppress tumor growth and generated synergistic tumor suppression effects when combined with anti-PD-1 treatment. Specifically, MAO-A restrains antitumor T cell immunity through controlling intratumoral T cell autocrine serotonin signaling. Apart from β -blockers and MAOIs (Wang et al., 2021), the results from preclinical studies provide a rationale for testing this combinatorial strategy in cancer patients.

The first prospective study on the combination of immunotherapy and a neurotransmitter receptor antagonist drug was conducted in melanoma patients (De Giorgi et al., 2018; Gandhi et al., 2021). It was shown that the patients taking propranolol, an approved non-selective β -blocker, not only had an 80% risk reduction for recurrence but also tended to be more sensitive to anti-PD-1 treatment (De Giorgi et al., 2018). The enhanced therapeutic efficacy of immune checkpoint inhibitors by β -blocker was also observed in lung cancer patients. The use of β -blockers was significantly associated with improved progression-free survival among non-small-cell lung cancer patients treated with SP-142, a PD-L1 inhibitor (Oh et al., 2021).

Pancreatic cancer is among the most immune-resistant tumor types. Given the potential role of neurotransmitters in the immunosuppressive microenvironment of PC, drugs targeting neurotransmitter signaling may help to limit immune suppression and overcome immunotherapy resistance in PC. The combination of neurotransmitter signaling-targeted drugs and immunotherapy is believed to provide new hope for PC patients (Balachandran et al., 2019).

CONCLUSION

Pancreatic cancer has the unique characteristic of increased neural density. As the messenger molecules, neurotransmitters have emerged as components with significant importance in

the TME of pancreatic cancer. Neurotransmitters can directly bind to the cancer cells, generating either promoting or inhibition effects on cancer growth. Meanwhile, the expressions of neurotransmitters and their corresponding receptors in the tumor-infiltrating immune cells imply a complicated relationship between the neurotransmitters and the immune cells in the TME. Further investigation on how neurotransmitters crosstalk with immune cells at the TME level will be of great interest, for it will facilitate our understanding of the mechanism behind the suppressive immune microenvironment of cancer. The tumor immune microenvironment contributes a lot to the initiation and development of cancers, as well as the response to cancer treatments, notably the immunotherapy. Nowadays, immunotherapy is increasingly involved in cancer therapeutic regimes. Breaking immune tolerance using specific receptor antagonists of neurotransmitters is possibly a promising strategy for combinatorial therapy with immune checkpoint inhibitors in PC. It is also plausible that modulating the expression of neurotransmitter receptors on the surface of CAR-T cells may promote the efficacy of CAR-T therapy. Further research into the precise mechanism of how immune cells regulated by different types of neurotransmitters in the TME might open up new avenues toward adjunct therapy against PC.

AUTHOR CONTRIBUTIONS

YL wrote the manuscript. HL searched the literatures, made the tables, and polished the language. HT and YG conceived the idea and revised the manuscript. All authors read and approved the final manuscript.

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