REVIEW ARTICLE

Pathology and Molecular Mechanisms of Perineural Spread of Tumors

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Abstract

Perineural invasion (PNI) is an important but under-reported route of metastasis of many cancers, in which neoplasm invades and spreads along the nerves. In recent years, PNI has been identified to contribute to the pathology of malignant tumors in the breast, stomach, head and neck, pancreas, prostate and large intestine. PNI of neoplasm may be attributable to poor prognosis of the patients, and sometimes appears to be the only cause of long-distance metastasis. Recent studies have furnished latest insights into the pathology and clinical features of PNI, characterized by continuous and interlinked multiple steps, starting from the formation of a perineural niche, comprising of neural cells, inflammatory cells, stromal cells, extracellular matrix, and blood vessels, in addition to the cancer cells. The critical step of PNI involves the establishment of connections between tumor and nerve through a number of signaling pathways consisting of soluble factors such as nerve growth factor, interleukins, and matrix metalloproteinases. Upon invasion into the nervous system, the cancer cells bring changes to neural cells and their microenvironment, leading to neoplastic spread along the nerves and alteration of normal nerve functions. In this review, we attempt to comprehensively cover the cellular and molecular mechanisms of perineural spread of tumors.

Keywords: Perineural invasion, Tumor, Perineural spread, Neoplasm, Perineural niche

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Introduction

Perineural spread of tumor may be well-defined as an expansion of the prime tumor through the neural sheath tissues (perineurium and epineurium) of a nerve[1]. It is well-accepted that typical routes of malignant tumor metastasis and invasion are blood and lymphatic vessels [2]. Perineural spread of tumors, in which neoplasm invades and spreads along the nerves, is a relatively under-studied process of cancer progression even though nerves were established to be involved in epithelial cell adenoma and later on in breast, bladder, pancreatic and colorectal tumors about three decades ago[3-7]. Initially described as the invasion of cancer cells near or passing through tumor nerves[2, 8], perineural spread of cancer cells was termed perineural invasion (PNI) by Batsakis in 1985 when the characteristics of this unique route of tumour invasion began to draw the attention of oncologists. PNI is now recognized as a distinctive pathological entity attributable to distant tumour spread beyond local invasion[8]. Mechanistically, PNI may involve reciprocal signalling interactions between nerves and tumor, and the invading cancer cells may have acquired the ability to respond to pro-invasion signals within the peripheral nerve milieu [9, 10]. The axon part of neuron is covered by a covering sheath known as neurolemma which is made up of epineurium, perineurium and endoneurium from outside to inside respectively. Nerves can grow in the direction of a tumor in various patterns, such as concentric lamellar, complete surrounding, partial surrounding, and tangent contact. PNI could be the sole route of tumor spread in the absence of all other routes[10]. Chronic initiation of the sympathetic nervous system by enhanced norepinephrine levels in the tumor microenvironment has been responsible for tumor spread. Neoneurogenesis is another key driver for progression of tumor[11, 12]. PNI has been shown as a pathological feature in cancers of multiple organs including stomach, large intestine, pancreas, head and neck, accompanied by low survival rates of the patients[10]. It is therefore important to take PNI into consideration while studying cancer pathology and devising better personalized point of care therapies in PNI patients.

Multistep and continuous process of PNI

The importance of PNI in cancer is evident from its widespread occurrence in various organs of the body **(Table 1)**. Previously, it was thought that PNI was a relatively less common route of cancer invasion and metastasis, requiring the availability of a "low resistance channel"[13, 14]. Based on the aforementioned hypothesis, PNI occurs only when the tumor is present in close proximity to the nerves, and neoplastic cells gain entry into the low resistance and cells-free perineural space with the help of nerve sheath and surrounding lymphatics. As research into the pathology of PNI deepens, evidence begin to support that occurrence of PNI involves multiple steps and a variety of factors [2]. A new hypothesis of tumor neural connects (TNC) [14] was developed to explain that the presence of a complex signaling network between tumor and nerve is chiefly responsible for the initiation of PNI **(Figure 1)**. This complex signal network is produced by a number of factors including, supporting cells, inflammatory cells, immune components, blood vessels and the extracellular matrix. Additionally, number of soluble signal molecules and their receptors are discovered to take part in the process [15], including interleukin 6 (IL-6) [16], matrix metalloproteinases (MMPs) [17], nerve growth factor (NGF) [18], and glial cell line-derived neurotrophic factor (GDNF) [19].

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Table 1: Importance of PNI in cancer of different organs of the body

PNI in cancer of different organs	**Recurrence rate**	**Prognosis**	**References**
Adenocarcinoma of the pancreatic duct	70%-100%	Poor	94-98
Stomach carcinoma	6.8%-75.6%	Poor	99-102
Prostate cancer	83.6%	Poor	103-105
Cervical cancer	8.6%-31.3%	Shortened disease-free survival time	106-108
Biliary tract cancer	56%-88%	28% patients survived up to 5 years	108 107
Colorectal cancer	15.7%-38.9%	Poor	109-112
Head and neck cancer	30-100%	Poor	113, 114

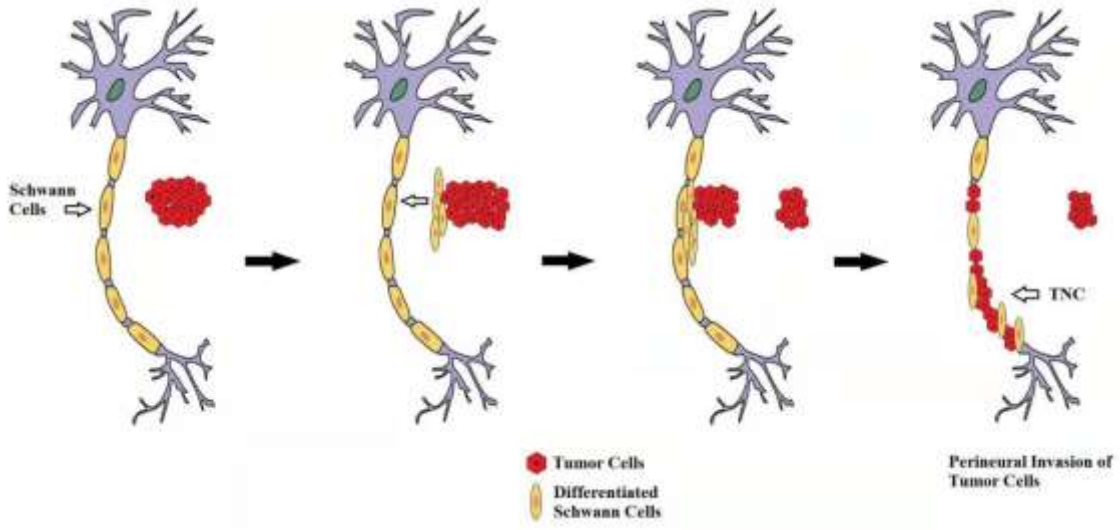

Figure 1: Schematic representation of perineural spread of cancer cells. Depicted are formation of tumor-neural connect (TNC) and spread of tumor cells into neuronal axon

PNI is a continuous and multistep process[20, 21]. The initial step is the direct interaction between cancer cells and nerve cells. The interaction is apparently bilateral: both the growth of a tumor to engulf a branch of nerves as well as the in-growth of nerves into a nearby tumor are observed [22]. A number of interlinked events include survival of neoplastic cells, neural formation, initiation of inflammation, recruitment of neoplastic cells to the nerves, regeneration of nerves, binding of neurolemma with tumor cells and, eventually, cancer cell invasion into the nerve. Apart from these fundamental steps, variation in supporting cells, nerve cells and perineural matrix, increased tumor cells

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invasion, neogenesis of nerve cells, interaction of tumor cells with nerve cells and escape of tumor cells from apoptosis, are also associated with PNI [23].

Nerve-Tumor Interaction

Growth and extension of axon and increased thickening of nerve fibers are the main steps in the interaction of nerve and tumor. The production of growth factors and neurotrophic factors in response to the nerve-tumor interaction leads to nerve growth in tumor, axon lengthening and nerve thickening[24]. Using nerve innervated mouse prostatic epithelial cells to study histological and genetic aspects of tumor, it was shown that the innervated integral nerves of tumor play a primary role in cancer development [25]. Usually characterized by abnormal energy metabolism pathways and high ratio of cancer cell cytoplasm; when the tumor was denervated, reduced cancer cell cytoplasm, condensed chromatin, and increased cancer cell apoptosis occurred [26]. Similar observations were made with mouse prostate cancer [27] and stomach cancer cells [28]. These findings indicate that the innervation of tumors and tumor invasion into the nerves may take place simultaneously during the course of PNI.

The importance of neurotransmitters in PNI has been underscored by numerous studies. The products of sympathetic nervous system (adrenergic fibers) and parasympathetic system (cholinergic fibers) participate in the initiation of tumor succession and tumor invasion, respectively [28]. Two important nerve cell protein families, namely neuroligins and neurexins, affect the communication between nerve cells and blood vessels[29, 30]. Two subtypes of neuroligins, NLGN1 and NLGN2, affect the glutamic acid reaction and secretion of catecholamine, respectively [31].

More recent studies focus on the relation of micro RNA (miRNA) and long non-coding RNA (lncRNA) with PNI. Abnormal expression of lncRNA-associated lung adenocarcinoma transcript 1 (lncRNA-MALAT-1) has been reported in several types of cancers, such as in hilar cholangiocarcinoma, linking the occurrence of PNI to tumor progression and metastasis[32]. Increased expression of lncRNA-MALAT-1 is also implicated in PNI in colon cancer [33] and renal cancer [34]. Similarly, upregulated expression of miR-21 in oral tumor is associated with depressed expression of phosphatase and tensin homolog, promoting PNI by allowing invasion and dispersion of tumor cells in nerves, leading to a poor survival rate of patients[35]. High levels of miR-21 but low levels of miR-100 and miR-125b are shown to occur in head and neck squamous cell carcinoma, again facilitating PNI [36]. In breast cancer, PNI is promoted by high levels of miR-370 [37]. Developing the miRNA based prophylaxis for PNI tumors can be a major breakthrough, preventing poor prognostic rates.

The Role of Schwann Cells in PNI

Regeneration of axons and survival time of transformed nerve cells are promoted by Schwann cells (also known as neurogliocytes). Movement of Schwann cells towards the tumor was described prior to the occurrence of PNI[38]. Acted upon by glial fibrillary acidic protein of Schwann cells, cancer cells can break up from a tumor mass and migrate towards Schwann cells, promoted by neural cell adhesion molecule 1 (NCAM-1) [39]. Additionally, Schwann cells secrete soluble signal molecules (chemokines, growth factors, biologically active small molecules and cytokines), that enhance the alteration of extracellular matrix, invasion of newly formed nerves, axon growth, tumor cell survival and neogenesis of damaged nerves [40]. Schwann cells have also been reported to induce salivary adenoid cystic carcinoma (SACC) cells to change into

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mesenchymal form through the action of brain derived nerve growth factor (BDNF) or tropomyosin receptor kinase B (TrkB), indicating that the Schwann cells are highly capable of enhancing the epithelial mesenchymal transition (EMT), aiding cancer invasion and metastasis [41, 42]. Moreover, the occurrence of mesenchymal epithelial transition (MET) has been reported when Schwann cells were cultivated with pancreatic cancer cells; upregulation of membrane expression of E-cadherin protein and down-regulation of vimentin and small mothers-against-ecapentaplegic (SMAD-3) proteins expression were detected during this interaction[43]. Decreased expression of SMAD3 is associated with activation of transforming growth factor β (TGF-β), apparently enhancing the migration of neoplastic cells [44].

Microenvironmental Factors Involved in PNI

An altered microenvironment is characteristic of PNI. This includes the occurrence of immature collagen and accumulation of fibroblasts in the extracellular matrix [45], low oxygen levels, enrichment of inflammatory cells, high glucose levels, and activation of sympathetic nervous system [23]. Hypoxia in the tumor leads to activation of hypoxia inducible factor 1α (HIF-1α) that accelerates the neogenesis of blood vessels [46] and the induction of the gene expression of chemokines and their receptors such as CXR4, CXCL12 and CX3CR1, which leads to upregulation of stem cell factor (SCF) and vascular endothelial growth factor (VEGF)[47] . Additionally, glucose transfer and glycolytic enzyme expression are enhanced by glucoamylase 1 (GLU-1) upregulation[48, 49]. Moreover, neoplastic cell resistance to apoptosis and increase in cell proliferation rates are strengthened by increased activity of telomerase reverse transcriptase(TERT) and surviving enzymes. These changes apparently attribute to PNI[49]. Furthermore, the activation of sympathetic system also leads to an increase of norepinephrine levels in the tumor microenvironment, which in turn gives rise to upregulation of chemotactic promoter by β-adrenergic receptor signal transduction pathway, facilitating the tumor growth [50]. Axonal sprouting, nerve homeostasis and dendritic growth are the roles played by the key factors that are secreted from Schwann cells, neurons, cytokines and growth factors in a perineural microenvironment, which ultimately endure and initiate cancer metastasis and invasion[20, 51] **(Figure 2)**.

Other types of cells in the tumor that facilitate tumor growth may also promote PNI. For instance, in pancreatic tumor, pancreatic stellate cells may play a key role. Activation of pancreatic stellate cells along with Matrix Metallopeptidase 2 (MMP-2) and MMP-9 enzymes, is induced by Sonic Hedgehog (SHH) transcription pathway. As the stellate cells and fibroblasts cover the pancreatic tumor cells in microenvironment, their activation by SHH leads to increased tumor invasion and tumor cell survival [52]. Fibroblasts also play key role in tumor invasion by synthesizing chemotactic factors, growth factors and perineurium sheath [2]. Macrophages play role in PNI; more accurately, a subgroup of macrophages which is known as endoneurial macrophages, is responsible for the neogenesis of damaged nerves and continuity of nerve action in steady state. Pancreatic tumor cells secrets Macrophage Colony Stimulating Factor 1 (MCSF-1) which leads to the invasion of macrophages towards the chemical signals, hence promoting the PNI [51].

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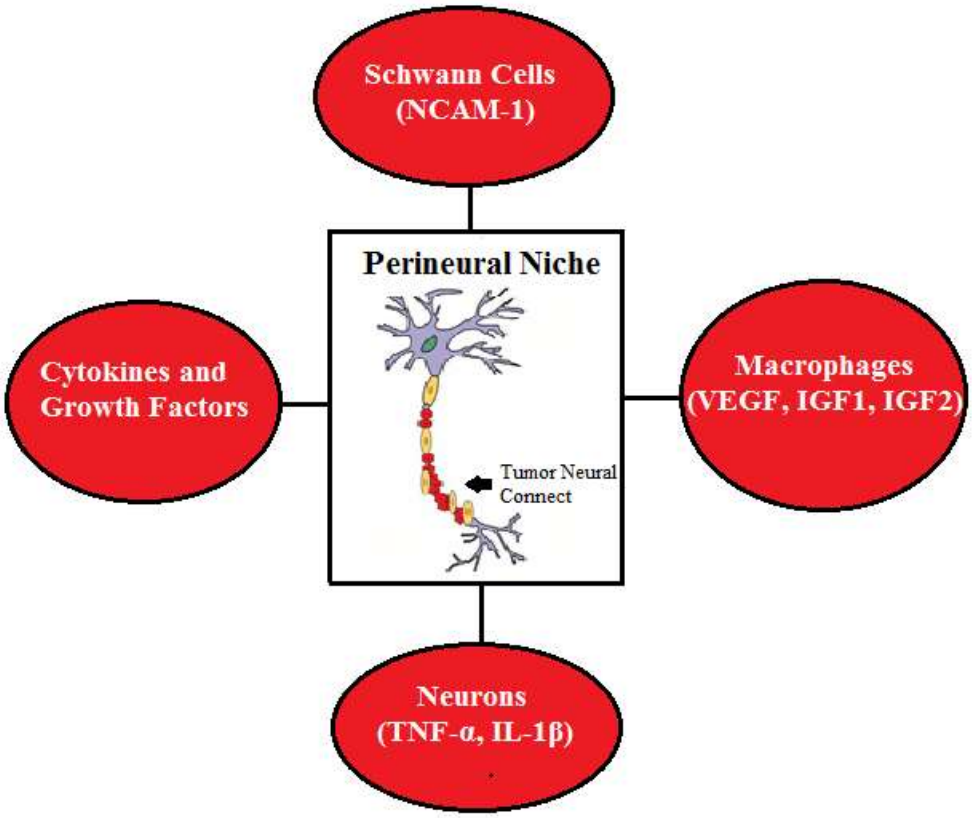

Figure 2: Key cells involved in Perineural Niche that can potentially facilitate cancer invasion

Medkine, Pleiotrophin, and Metalloproteinases in PNI

Medkine (MDK) and pleiotrophin (PTN) of heparin binding growth factor family are implicated in PNI. It was shown that binding of PTN to its high affinity receptor N-syndecan causes neovascularization, which facilitates growth of tumor cells and axons, and thus promote PNI [53, 54]. Upon the invasion of tumor cells into pancreatic nerves, Schwann cells and main nerve cells release N-syndecan. The PTN-N-syndecan complex causes the influx of more PTN-activated cells to the nerve [55]. Similarly, the binding of MDK to the syndecan-3 receptor stimulates lymphatic metastasis of cancer cells, promoting PNI as a result[56]. Upregulated expression of the Zinc-dependent endopeptidase family of matrix metalloproteinases (MMPs), which are involved in tissue remodeling and degradation of extracellular matrix, has been linked to the occurrence of PNI in stomach cancer, lung cancer, liver cancer, breast cancer, pancreatic cancer and cholangiocarcinoma[57-59]. Specifically, extracellular signal regulated kinases (ERK)/MAPK pathway is shown to be responsible for the phosphorylation of ETS1 gene by β6 integrin which induces MMP-3 and MMP-9 expression, leading to PNI[60]. In another study, PNI of stomach cancer was found to be promoted by higher expression of phosphorylated epidermal growth factor receptor (EGFR), MMP7 and ERK1/2 [61]. The mechanisms of MMP-promoted PNI include invasion of tumor cells facilitated by the degradation of extracellular matrix and reduced adhesion of tumor cells, inhibition of apoptosis and upregulation of tumor cell proliferation, activation of EMT, promotion of metastasis of cancer cells by activating

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growth factors, and upregulation of tumor angiogenesis[62-70].

Few other molecules involved in the process of PNI are survivin, slug, galanin, neuropeptide Y and substance P **(Table 2)**. Survivin has been recently reported to block the mitochondrial function and receptor's apoptosis, thus block the tumor cell apoptosis[71]. Slug is the member of Zinc Finger Transcription Factor (ZFTF) family and found to promote PNI throught the enhancement of EMT process by blocking E-cadherin and positively regulating the MMP promoting factors [72, 73]. After binding to the galanin receptor 2, Galanin promotes the transcription of cyclooxygenase-2 (COX-2) to produce prostaglandin E2 (PGE2). Consequentially, perineural invasion is promoted by increased production of PGE2[24, 74]. The neuropeptide Y is produced and secreted by affected nerve cells and tumor cells itself[75]. Substance P is not only responsible for distant invasion of neoplastic cells by activating MAPK pathway but is also related to the pain associated with tumor[76]. A host of growth factors and cytokines, produced in the tumor microenvironment by tumor cells and non-tumor cell, have been described to support the mechanism of neural tracking in which cancer cells show capacity to actively migrate alongside nerves.

Table 2: Molecules involved in the process of PNI

Molecules/Cytokines Involved	**Major Role**	**Mechanism**	**Expression**	**Ref.**
SURVIVIN	Anti-apoptotic	Blocks the mitochondrial function & receptor's apoptosis	High, especially in Pancreatic cancer	[71]
SLUG	Enhance EMT, regulation of the MMP	Blocks E-cadherin	High in basal layers of Epidermis	[72, 73, 115]
Galanin	Increased production of PGE2	Transcription of COX-2)to produce PGE2, after binding to the galanin receptor 2	Down regulated in gastric cancer	[24, 74, 116]
Neuropeptide Y	Angiogenesis	Act via malleability of NPY receptors	High in adrenal cortical tumors	[75, 117, 118]
Substance P	Angiogenesis & distant invasion of neoplastic cells	Activates the MAPK pathway	High in colorectal cancer	[119, 76, 120]
Nerve growth factor (NGF)	Neurogenesis	Uptake of neurotrophic factor by nerve terminals	High in Breast Cancer	[18, 121, 122]

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Glial cell line-derived neurotrophic factor (GDNF)	Proliferation, migration of enteric progenitors, differentiation of neurons	Neurotrophic action via GDNF/GFRα/Ret complex formation	Human pancreatic cancer cells	123 19, 124-126
Neural cell adhesion molecule (NCAM)	Neural development	Homophilic, Ca2+-independent, binding mechanism	Small-cell lung carcinoma and neuroblastoma	127-130
Matrix metalloproteinases (MMPs)	Morphogenesis	Degrade ECM proteins during the process of cancer metastasis and invasion	Human breast cancer	17, 131-133
Tumor Necrosis Factor (TNF-α)	Carcinogenesis	Induces IL-6 release through the inhibitory kappa B (IκB)-nuclear factor kappa B (NFκB) pathway	High in Ovarian cancer, Breast cancer, prostate cancer	134-138
Interleukin 6 (IL-6)	Protumorigenic effect	Agonist for cells expressing gp130. Induce the transcription of factors in many paths of inflammation	Prostate cancer	139-141
Transforming Growth Factor β (TGF-β)	Invasion and metastasis by Increased TGF-β1 mRNA in cancers	Induce epithelial-mesenchymal transition	High in Breast cancer	142-144
Interleukin 10 (IL-10)	Pro- and antitumoral effects	Inhibits NF-κB signalling	High in cervical cancer	145, 146

Neurotrophin factors

Neurotrophin factors produced by tumor cells and nerve tissues are important protein molecules for the regulation of tumor nerve generated signal pathway, growth and survival of nerves associated with tumor. Nerve Growth Factor (NGF) integrates with Tyrosine Kinase (Trk) high affinity receptor and p75 Neurotrophin (p75NTR) low affinity receptors are expressed in tumor cells. This activated NGF in tumor cells and nerve sheath contributes to its important role in PNI by forming the axons, differentiating the nerves and enhancing the damaged nerve survival time[77-79]. Expression level of NGF can vary in different conditions; in case it is overexpressed it can reduce the apoptosis of tumor cell of pancreas, enhance the proliferation of nerves, boost up the TrkA

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signal, enhances the MMP-2 and also activates the Mitogen Activated Protein Kinase (MAPK) p44/42 signal pathway. In short, overexpression of NGF leads to PNI of pancreatic cancer[49]. In a study, negative feedback is also shown with respect to the NGF-TrkA pathway; reporting that the pathway helps the tumor cells to survive and migrate to the dorsal root ganglia but upon reaching there, the occurrence of PNI gets reduced due to inhibition of NGF-TrkA pathway by neutralizing antibodies and interfering RNA[80]. Neurotrophin 3 (NT-3) and TrkB are high affinity receptors of Brain Derived Neurotrophic Factor (BDNF); this neurotrophin-receptor complex promotes PNI and poor prognosis by production of MMP-2 from tumor cells. *In vitro* studies showed that growth and advancement of pancreatic and prostatic cancer in mouse was stopped by blocking the NT-3 receptor[81-84]. The survival of many types of neurons in humans is potentially promoted by a small protein "Glial Cell Derived Neurotrophic Factor" (GDNF). Other three members of same family are neurturin, artemin and persephin. Survival of tumor cells, differentiation of nerves, axon growth and signal pathways of growth are related to GDNF. For its expression in tumor, GDNF uses its receptor GFRα1/RET and it has been reported that the occurrence of PNI was reduced by blocking the GFR receptor[85, 86]. Nerves and macrophages secrete GDNF, that forms GDNF-GFRα1 complex after binding with GFR receptor. A gene of tumor cells known as "Rearranged During Transfection gene" (RET), binds with GDNF-GFRα1 complex and controls the metastasis of cancer cells, enhances the invasion, initiates the MMPs excitation, growth of axons and ultimately increases growth of cancer cells by activating MAPK pathway through the induction signal transduction pathway[20, 51, 87, 88]. Similar to GDNF, the second member of same family, artemin also uses a GFR receptor (GFRα3) to form a complex and expressed in pancreatic cancer leading to PNI [89].

Perspectives

The function of systemic therapies in the controlling perineural spread and perineural invasion remains uncertain. Treatment procedures for patients with PNI have not been recognized. A study revealed that after a median time of 21 months, treatment on PNI with surgery followed by radiation therapy and chemotherapy, 1/3rd of patients died from the disease[90, 91]. There is a versatile technology called as CRISPR associated protein 9 (CRISPR/ Cas9), in a sequence-specific manner delivers the capacity to enhance or eliminate DNA in the genome[92, 93]. Vigorous research is required, proceeding to increase the efficacy of CRISPR/Cas9 targeting. Schwann cells show affinity to cancer cells, and secret soluble signal molecules (chemokines, growth factors, biologically active small molecules and cytokines)[22]. Therefore, targeting these signal molecules can inhibit nerve invasion. Considering the range of benign procedures that may look like perineural connection, might assist to prevent excessively aggressive treatments, diagnostic misperception, and misdiagnosis. Efforts should be made to explain the utmost common patterns of spread to increase treatment results but reducing the effects of radiation.

Perineural invasion (PNI) has attracted the attention of cancer researchers as an important aspect in tumor invasion and metastasis. The process involves interlinked multiple steps, beginning from the development of a perineural niche, which includes inflammatory cells, neural cells, supporting cells, and blood vessels. A number of signalling pathways have been identified, as well as many soluble protein factors and extracellular matrix components that act to connect tumors and the nerves. PNI is now recognized as an important feature in the

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pathology of malignant tumors of several organs, in which neoplasm invades and spreads along the nerves, yet it is under-stated route of cancer metastasis. As this perineural invasion raises disease sternness, an improved consideration of how the process is controlled may benefit in the improvement of therapeutics aiming at tumor-neuronal connections. Identification of new molecular mechanisms of PNI will undoubtedly emerge from in-depth research in this field, opening gates to new approaches in more personalized cancer treatment.

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