World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i39.6555

World J Gastroenterol 2013 October 21; 19(39): 6555-6558
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Pleiotrophin promotes perineural invasion in pancreatic cancer

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Author contributions: Yao J and Feng XS conceived and designed the study, did literature search and wrote the manuscript; Yao J and Hu XF were involved in the manuscript writing; Gao SG designed the study and wrote the manuscript; all authors have read and approved the final version to be published.

Supported by National Natural Science Foundation of China, No. U1204819; and Health Science and Technology Innovation Talents Program of Henan Province, China, No. 4203

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Received: June 14, 2013 Revised: July 19, 2013
Accepted: August 5, 2013
Published online: October 21, 2013

Abstract

Perineural invasion (PNI) in pancreatic cancer is an important cause of local recurrence, but little is known about its mechanism. Pleiotrophin (PTN) is an important neurotrophic factor. It is of interest that our recent experimental data showed its involvement in PNI of pancreatic cancer. PTN strongly presents in the cytoplasm of pancreatic cancer cells, and high expression of PTN and its receptor may contribute to the high PNI of pancreatic cancer. Correspondingly, PNI is prone to happen in PTN-positive tumors. We thus hypothesize that, as a neurite growth-promoting factor, PTN may promote PNI in pancreatic cancer. PTN is released at the time of tumor cell necrosis, and binds with its high-affinity receptor, N-syndecan on pancreatic nerves, to promote neural growth in pancreatic cancer. Furthermore, neural destruction leads to a distorted neural homeostasis. Neurons and Schwann cells produce more N-syndecan in an effort to repair the pancreatic nerves. However, the abundance of N-syndecan attracts further PTN-positive cancer cells to the site of injury, creating a vicious cycle. Ultimately, increased PTN and N-syndecan levels, due to the continuous nerve injury, may promote cancer invasion and propagation along the neural structures. Therefore, it is meaningful to discuss the relationship between PTN/N-syndecan signaling and PNI in pancreatic cancer, which may lead to a better understanding of the mechanism of PNI in pancreatic cancer.

Key words: Pleiotrophin; N-syndecan; Neurite outgrowth; Perineural invasion; Pancreatic cancer

Core tip: We discussed the important novel role of pleiotrophin (PTN) in perineural invasion (PNI) of pancreatic cancer, an important cause of local recurrence. Our recent experimental data demonstrated the involvement of PTN in PNI of pancreatic cancer. PTN strongly presents in the cytoplasm of pancreatic cancer cells, and high expression of PTN and its receptor may contribute to the high PNI of pancreatic cancer.

Yao J, Hu XF, Feng XS, Gao SG. Pleiotrophin promotes perineural invasion in pancreatic cancer. *World J Gastroenterol* 2013; 19(39): 6555-6558 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i39/6555.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i39.6555

INTRODUCTION

Pancreatic cancer is one of the most malicious human malignancies with the lowest 5-year survival rate[1-3]. At the time of diagnosis, most patients have locally advanced disease and/or distant metastatic lesions precluding radical operation resection[3-5]. Perineural invasion (PNI) is considered as an important factor of aggressive tumor

behavior, and it is associated with local recurrence and poor outcome of pancreatic cancer[6]. Pancreatic cancer cells frequently have intimate contact with intrapancreatic nerves and thereby alter, invade, and damage the intrapancreatic nerves[7]. PNI extending into the extrapancreatic nerve plexus is a histopathologic characteristic in pancreatic cancer, which leads to abdominal pain and retropancreatic tumor extension[8-10]. PNI is defined as presence of cancer cells within the epineural, perineural, and endoneurial spaces of the neuronal sheet and around the nerves[11,12]. It precludes curative resection, promotes local recurrence, and finally negatively influences the prognosis of the patients. However, the mechanisms of the alteration and invasion of pancreatic nerves and the spread of cancer cells along pancreatic nerves in pancreatic cancer remain poorly understood. Therefore, neurotrophic factors are of interest because recent experimental data showed their involvement in neuro-cancer interactions in pancreatic cancer[13].

MECHANISM OF PNI IN PANCREATIC CANCER

The mechanism of PNI in pancreatic cancer is unclear, although it can be partially explained by the anatomical proximity of the pancreatic and celiac artery neural plexus. The perineurium is believed to be deficient near the nerve ending, at the site invaded by the blood vessels in the nerves, and at the site invaded by reticular fiber[14]. Another possible explanation of PNI in pancreatic cancer is neurotropism because some advanced cancers with PNI express numerous types of neuroendocrine markers including S-100, Synaptophysin, substance P, enkephalin, and neural cell adhesion molecules[15]. Other specific factors such as nerve growth factor also enhance the cancer-nerve interaction, providing biological and physical parameters that would explain their frequent and intimate relationship[16].

PLEIOTROPHIN-CANCER INTERACTION

Pleiotrophin (PTN) is a neurotrophic factor, also known as the neurite growth-promoting factor. The protein is mainly expressed during early embryogenesis. In human adult tissues, it is markedly down-regulated and present only at minimal levels in very few tissues. PTN is a 136-amino-acid long secreted cytokine related to diverse biological properties, including neuritis outgrowth, angiogenesis, and tumor growth[17,18]. It is strongly expressed in different human tumor cells, and expression of the PTN gene in tumor cells *in vivo* accelerates growth and stimulates tumor angiogenesis[19,20]. Experimental evidence from different laboratories also supported the potential of PTN to play an important role in promotion of human tumors. PTN transcripts are highly expressed in a high proportion of different human tumor samples, including pancreatic cancer, breast carcinoma, melanocytic tumor, carcinoma of the prostate, glioblastoma, and astrocytomas[21-25]. Cell lines derived from these tumors have constitutive activation of the endogenous *PTN* gene, while PTN expression is not detected in non-tumor cell lines of the same origin and in the non-tumorous tissues[26].

ASSOCIATION BETWEEN PTN AND PANCREATIC CANCER

PTN is not expressed in normal pancreatic tissues, but it is highly expressed in pancreatic cancer tissues and correlates with pancreatic cancer progression[27]. In previous experiment, we studied PTN and its receptor N-syndecan protein levels in 38 patients with pancreatic cancer by immunohistochemistry, analyzed for its correlation with clinicopathological features, PNI, and prognosis. The results suggested that PTN was strongly present in the cytoplasm of pancreatic cancer cells; N-syndecan was intensely present in the perineurium of pancreatic nerves but not in the cancer cells. PTN combined with N-syndecan might have contributed to the high level of PNI and poor prognosis of pancreatic cancer[28]. Furthermore, tissue expression of PTN resulted in its elevated serum levels in more than 50% of the pancreatic cancer patients, and a statistically significant positive association was found between elevated serum levels of PTN at the time of surgery and its expression by tumors[27]. In both mice and humans, serum PTN levels dropped after successful tumor removal, suggesting that PTN may represent a new tumor marker in pancreatic malignancies.

PTN-NERVE INTERACTION

PTN was initially isolated from neonatal rat brain as a neurite outgrowth-promoting protein. Previous studies have demonstrated that N-syndecan acts as a receptor in PTN-induced neurite outgrowth in perinatal rat brain neurons[29]. N-syndecan-stably-transfected N18 neuroblastoma cells showed clearly enhanced neurite outgrowth upon contact with PTN-containing substrate. PTN and N-syndecan utilize the cortactin-src pathway for the intracellular signaling in neurite outgrowth[30].

PTN promoted neurite outgrowth from different cultured neuronal cell types, including cultures of embryonic and perinatal cortical neurons, neuroblastoma cells, and PC12 cells[31], and anti-PTN antibodies inhibited neurite outgrowth *in vitro*[29]. The addition of PTN to donor cells resulted in better functional recovery and better survival of dopaminergic neurons, owing to the decrease of cell death after transplantation[32]. The results revealed that PTN had effects on donor cells in neural transplantation both *in vitro* and *in vivo*. In adult animals, PTN expression was lower but increased during recovery from injury, playing a major role in the cell growth and differentiation associated with tissue regeneration. A higher PTN level was noticed in sciatic nerves within a few days after crush injury when axon regrowth was induced, whereas PTN level was lowered after the axons reached their target[33]. The increased PTN protein levels during the first step of

peripheral nerve regeneration suggested time-restricted synthesis of PTN within the injured nerve. These results suggested that PTN may be involved in peripheral nerve regeneration after the nerve injury.

PTN and N-syndecan act as a ligand-receptor pair in neurite outgrowth[34]. It is possible that PTN and its receptor act synergistically to promote PNI in pancreatic cancer. Our previous experiments also showed that recombinant adenovirus-mediated PTN-shRNA successfully silenced *PTN* gene expression in pancreatic cancer cells, and the neurite outgrowth of dorsal root ganglion neurons was evidently inhibited by knocking down the PTN protein[35,36].

CONCLUSION

Previous studies described the importance of individual neurotrophic factor in PNI in pancreatic cancer[37]; however, the mechanism of PNI was not clarified explicitly. Former studies of PTN focused on angiogenesis, neuritis outgrowth, and tumor growth[38,39]. There was no relevant report about the association between PTN and PNI in human tumors. Interestingly, elevated PTN expression has been found to be an essential autocrine and paracrine factor for various human malignancies, including pancreatic cancer, breast carcinoma, melanocytic tumor, carcinoma of the prostate, and astrocytomas[40]. Correspondingly, PNI is also prone to happen in these PTN-positive tumors. Therefore, we hypothesize that, as a neurite growth-promoting factor, PTN and N-syndecan act synergistically to promote PNI in pancreatic cancer. PTN is an important factor of the induction of neurite outgrowth, survival of neurons, and peripheral nerve regeneration under pathological conditions[30,31,41]. PTN is released at the time of tumor cell necrosis and binds with its high-affinity receptor, N-syndecan on pancreatic nerve, to promote neurite growth in pancreatic cancer. Furthermore, in pancreatic cancer, cancer cells infiltrate and destroy the perineurium of pancreatic nerves, and the neural destruction leads to a distorted neural homeostasis. Neurons and Schwann cells produce more N-syndecan in an effort to repair the pancreatic nerves. However, the abundance of N-syndecan further attracts PTN-positive cancer cells to the site of injury, creating a vicious cycle. Ultimately, increased PTN and N-syndecan levels, due to the continuous nerve injury, may promote cancer invasion and propagation along the neural structures.

FUTURE IMPLICATION

Pancreatic cancer is characterized by PNI, early lymph node metastasis, and poor prognosis. PNI is an important cause of local recurrence, but little is known about its mechanism. It is meaningful to discuss the relationship between PTN/N-syndecan signaling and PNI in pancreatic cancer, which will probably lead to a better understanding of the mechanism on PNI. Considering that the production of inhibitors for PTN and N-syndecan is at the stage of laboratory trials, we believe that such study has significant translational potential. Due to the unclear mechanism, it is difficult to improve or apply gene therapy targeting the possible candidate cancer genes. Therefore, understanding the relationship between PTN/N-syndecan signaling and PNI may contribute to an improved therapy of PNI in pancreatic cancer. In further studies, we will silence the *Ptn* gene in orthotopic pancreatic cancer model in nude mice using recombinant adenovirus-mediated PTN-shRNA, and investigate the effects of PTN on PNI of pancreatic cancer.

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ISSN 1007-9327