



## Review

# New insights into perineural invasion of pancreatic cancer: More than pain



Dingkong Liang<sup>1</sup>, Si Shi<sup>1</sup>, Jin Xu, Bo Zhang, Yi Qin, Shunrong Ji, Wenyan Xu, Jiang Liu, Liang Liu, Chen Liu, Jiang Long, Quanxing Ni, Xianjun Yu<sup>\*</sup>

<sup>a</sup> Department of Pancreatic and Hepatobiliary Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

<sup>b</sup> Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

<sup>c</sup> Pancreatic Cancer Institute, Fudan University, Shanghai, China

## ARTICLE INFO

## Article history:

Received 12 October 2015

Received in revised form 26 December 2015

Accepted 11 January 2016

Available online 12 January 2016

## Keywords:

Pancreatic cancer

Perineural invasion

Prognostic factor

Cancer microenvironment

## ABSTRACT

Pancreatic cancer is one of the most malignant human tumors. Perineural invasion, whereby a cancer cell invades the perineural spaces surrounding nerves, is acknowledged as a gradual contributor to cancer aggressiveness. Furthermore, perineural invasion is considered one of the root causes of the recurrence and metastasis observed after pancreatic resection, and it is also an independent predictor of prognosis. Advanced research has demonstrated that the neural microenvironment is closely associated with perineural invasion in pancreatic cancer. Therapy targeting the molecular mechanism of perineural invasion may enable the durable clinical treatment of this formidable disease. This review provides an overview of the present status of perineural invasion, the relevant molecular mechanisms of perineural invasion, pain and hyperglycemia associated with perineural invasion in pancreatic cancer, and the targeted therapeutics based on these studies.

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\* Corresponding author at: Pancreatic Cancer Institute, Fudan University, Department of Pancreatic and Hepatobiliary Surgery, Fudan University Shanghai Cancer Center, 270 DongAn Road, Shanghai 200032, China.

E-mail addresses: [yuxianjun88@hotmail.com](mailto:yuxianjun88@hotmail.com), [yuxianjun@fudanpci.org](mailto:yuxianjun@fudanpci.org) (X. Yu).

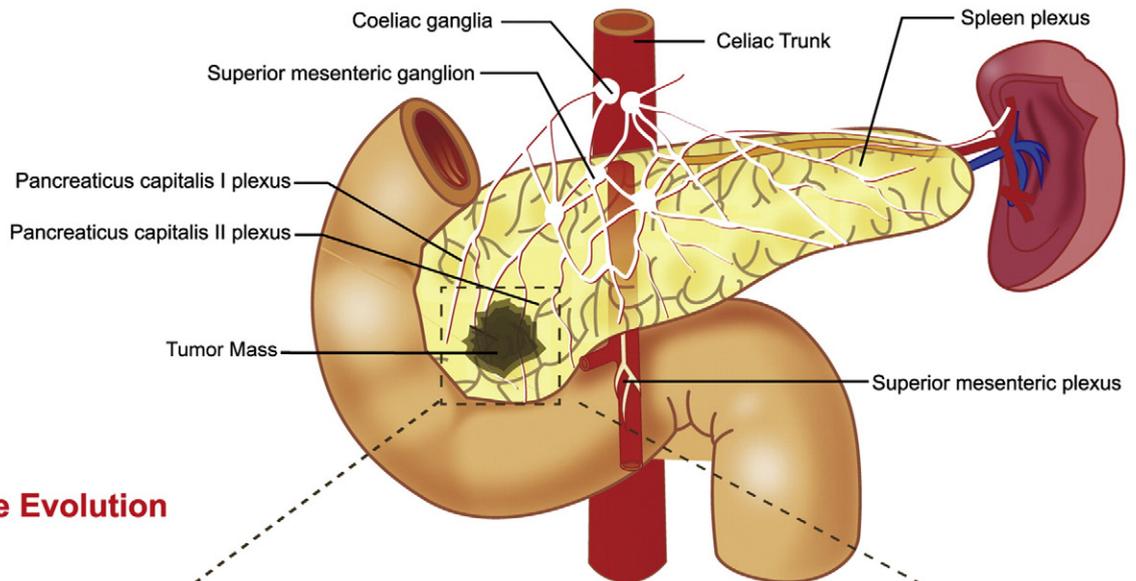
<sup>1</sup> These authors contributed equally to this article.

# PNI of Pancreatic Cancer

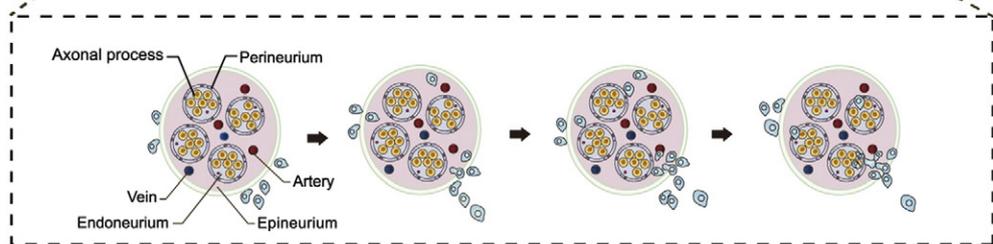
## A Clinical Symptoms

- ◇ Abdominal pain
- ◇ Tumor metastasis and invasion in the early phase
- ◇ Local postoperative recurrence
- ◇ Poor prognosis and decreased survival

## B Pathological Anatomy



## C Microstructure Evolution



## D Nerve Microenvironment

- ◇ Neurotrophins: NGF family, GDNF family
- ◇ Chemokines: CXCL12/CXCR4 axis, CX3CR1/CX3CL1 axis
- ◇ Matrix metalloproteinases: MMP-2, MMP-9
- ◇ PNI related cell: Tumor-associated macrophages, Schwann cells, Pancreatic stellate cells
- ◇ Related genes and proteins

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