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Brief Communication

Perineural invasion in pancreatic cancer: Current biological function in R status, prognosis, and pain

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is predicted to become the second leading cause of death in 2030 and it is characterized by poor prognosis, recurrence and resistance to therapies. Several factors contribute to the complexity of this disease, among those the invasion of nerves by PDAC cells. This condition, defined as perineural invasion (PNI), is responsible of PDAC progression and pain generation. To date, PNI emerges as a hallmark feature of PDAC, showing the same oncological weight of lymph node metastasis in terms of prognosis. Targeting PNI could help improve prognosis and pain relief in PDAC patients. Only recently, a severity scoring system has been proposed to quantify PNI in histological samples although prospective validation and standardization are strongly advocated. More information about peripancreatic soft tissue infiltration and a "true" curative surgery could be found in understanding the molecular mechanisms of PNI. The incorporation of PNI markers for grading mesopancreas and retroperitoneal invasion is required to overcome current limitations of the histological workup. We discuss the modern understanding of PNI in PDAC, and the state of the art in clinical setting. Although there are still a lot to learn about PDAC, PNI represents one of the biological detonators and an important focus of future research.

Pancreatic ductal adenocarcinoma (PDAC) is predicted to become the second leading cause of death in 2030 [1]. With a 5-year overall survival rate ranging from 10 % to 20 % [1,2], PDAC poses significant challenges in terms of prognosis. Interactions among PDAC cells, immune cells, blood vessels and nerves play pivotal roles on the retroperitoneal invasion [3]. A specific tropism for nerves and a complex neural influence have been reported in PDAC patients, with sensory and sympathetic nerves able to stimulate tumorigenesis, together with the protective effects of parasympathetic nerves [4–6]. Perineural invasion (PNI) is emerging as a hallmark of PDAC, characterized by cancer cell infiltration of at least 33 % of nerves along the epineural, perineural, and endoneural layers [7]. The prevalence of PNI is approximatively 70 %, reaching up to 100 % in specific cases [4,5,8,9]. The variation of PNI diagnosis depends on personalized experience of Pancreatic Unit and on the internal protocol adopted for pathological sampling, together with its examination by experienced pancreatic pathologists. This accuracy might be optimized by the development of radiomics and radiogenomics, and by the precision medicine applied to pathological analysis (histological severity score based on PNI). The mean area of nerves in PDAC tissues is almost four times greater than in normal tissue and nerve-positive patients have a higher risk of death compared to patients without nerve infiltration [6]. Microscopically, the density of the ganglia is more elevated in the pancreatic head as opposed to the body and pancreatic tail. In particular, a nerve invasion greater than 8 mm is linked to a high frequency of positive resection margin in PDAC patients [10]. Nerve infiltration is also a risk factor for patients without lymphatic spread, indicating a subgroup of N0 patients with an increased risk of death at an early age [6]. Nowadays, PNI can only be

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diagnosed after surgery. The ability to detect PNI preoperatively using medical imaging and accurate nerve topography would aid clinicians in devising operative strategies [11]. Furthermore, the potential for real time intraoperative navigation and identifications of PNI may in the future allow for personalized surgical removal of peripancreatic tissue [12]. The identification of predictive biomarkers to monitor the presence and severity of PNI are strongly advocated for two reasons: first for surgeons to perform tailored surgery in the contest of multimodal therapeutic approaches and the more appropriate timing and secondly, for oncologists to plan systemic treatments. Detectable even in early-stage PDAC, PNI could serve as a strong prognostic factor. In particular, PNI indicates poorer outcomes in patients with localized and early-stage cancer, without lymph node metastases [6]. Interest in targeting PNI in PDAC has increased in recent years, supported by promising preclinical results [7]. Biological studies have highlighted the predictive role of genes, such as *TNFRSF14*, *ATF3*, and *XPO1* in identifying PNI [13]. The pancreatic neurons supply norepinephrine (NE) which modulates the α2-adrenergic receptors (α2-AR) and an upregulation of nerve growth factor (NGF) by PDAC cells. NE/α2-AR interaction promotes PNI by inducing upregulating metalloproteases, MMP-2 and MMP-9 and epithelial–mesenchymal transition (EMT). Mucin-1 (MUC-1) and its receptor myelin-associated glycoprotein (MAG) are found in high levels in PDAC cells. Both of them participate in PNI by interacting with Schwann cells [8]. In addition, NE promotes pancreatic PNI through β-AR/PKA/STAT3 signaling [9] (Fig. 1). Interestingly, Celastrol a natural product with anti-inflammatory, anti-angiogenic, and anti-oxidant properties, has shown cytotoxic effect in PDAC cells mediated via over-expression of *ATF3* [14]. More specifically, the blocking of *XPO1* with Selinexor inhibits PDAC development in vitro and in orthotopic models [15]. Preclinical data suggest that the combination of Selinexor-GEM-nab-paclitaxel is as an effective therapy for metastatic PDAC [15]. To date, validation of PNI inhibitors has not been archived [7]. Future studies are needed to better define the role of PNI and its inhibitors in PDAC chemoresistance. On the other hand, a severity scoring system has been proposed to quantify PNI, although prospective validation and standardization are needed [16]. This score provides more comprehensive information on the caliber of nerves infiltrated by PDAC cells and the grade of PNI, whether focal or diffuse. Unfortunately, the lack of a validated PNI scoring system for grading infiltrated nerves has hindered accurate staging of PDAC patients. R status indicates the presence of malignant cells in the surgical margins of PDAC resections that are evaluated microscopically (biliary, pancreatic neck, and duodenal transection margins, anterior and posterior pancreatic margins, superior mesenteric groove and superior mesenteric artery margin) [1]. R0 (margin-free) resection is the final target of care that must to be reached after pancreatectomy for patients with PDAC. The definitions for R0 and R1 margin status after resection for pancreatic cancer are controversial and the reported R0/R1 rates and associated survival are heterogeneous [1,2,17]. Based on current recommendations and international guidelines, the achieving of R0 status after multimodal PDAC treatment is realistically achievable in less than 50 % of cases [1,2,17]. Recently, R status was confirmed as an independent predictor for overall survival and recurrence free survival after neoadjuvant chemotherapy and R1 resection is significantly associated with local but not distant recurrence [18]. More information on peripancreatic soft tissue infiltration that contains microscopic vessels and nerves, and a "true" curative surgery may be found in understanding the molecular mechanisms of PNI. Neoadjuvant therapies in resectable and borderline PDAC patients have survival benefits and improve postoperative long-term postoperative outcomes by controlling PNI [5,19,20]. In particular, FOLFIRINOX treatment has shown the most promising outcomes in reducing both PNI and the number of positive lymph nodes [5]. This suggests that current chemotherapy controls the spread of cancer cells and challenge the prognostic significance of the pathological staging design for upfront resections [5,20,21]. The surgical strategy needs to be changed in the contest of the timing of multimodal approaches. Results reported the benefits of neoadjuvant chemotherapies in reducing the rate of nodal metastases and the rate of PNI and microvascular invasion [19]. Neoadjuvant therapy is now the preferred approach for PDAC patients with resectable and borderline tumors [19]. It is undeniable that PNI has the oncological weight of lymph node metastasis in terms of prognosis. Overcoming the current limitations of histological workup, PDAC staging requires the incorporation of accurate biomolecular markers for grading mesopancreatic invasion. Together with its role in prognosis

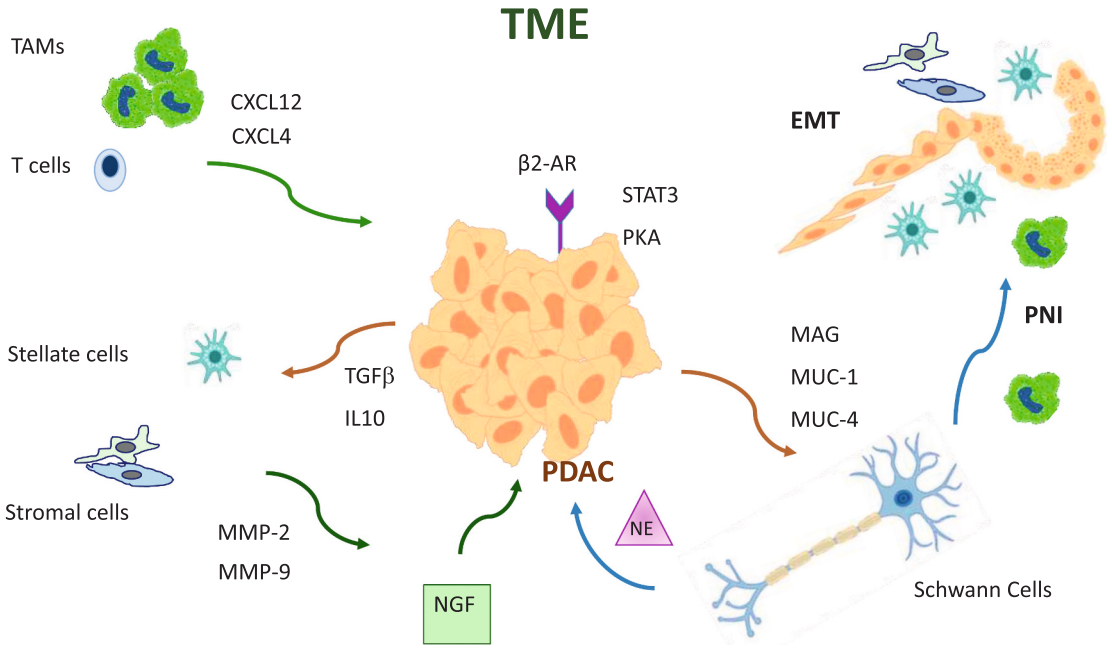

Fig. 1. PNI signaling in PDAC tumor microenvironment (TME). β2-adrinergic receptor (β2-AR), epithelial-mesenchymal transition (EMT), chemokine (C-X-C motif) ligand 4 (CXCL4), C-X-C motif chemokine 12 (*CXCL12*), interleukin (IL), matrix metalloproteinases (MMP-2, MMP-9), myelin-associated glycoprotein (MAG), nerve growth factor (NGF), norepinephrine (NE), protein kinase A (*PKA*), regulatory T cells (Treg), signal transducer and activator of transcription 3 (Stat3), transforming growth factor beta (TFG-β),transmembrane mucins (MUC-1 MUC-4), and tumor associated macrophages (TAMs).

and recurrence, nerves contribute to abdominal or back pain in PDAC patients [22]. Neurogenic inflammation is recognized as risk factor of pain generation in early PDAC stages and pancreatitis [7,23,24]. The neurogenic inflammation is responsible of pain in chronic pancreatitis. Neurotransmitters are increased in afferent pancreatic nerves showing a correlation between pain and immune cell infiltration. The neuro-immune interaction is an important factor for pain generation in acute and chronic pancreatitis [23–25]. Neuropeptides, ion channels, and the endocannabinoid are responsible of the auto-amplification loop between inflammation and pain during the progression of acute pancreatitis [25]. A well-documented correlation between nerve-growth factor (NGF) expression, PNI, and the level of pain sensation has been studied [8]. In PDAC patients, several neurotransmitters, including glutamate, Substance P, NGF, and calcitonin gene related peptide, have been implicated in the generation of pain [24]. While many issues in pancreatic cancer research remain to be addressed, the recognizing of the role of PNI as an integrated clinical marker will offer the potential to improve therapeutic protocols, tumor staging and pain relief in PDAC patients. Although there is still much to learn about the development and progression of pancreatic cancer, PNI in PDAC may be one of the biological detonators.

CRediT authorship contribution statement

Federico Selvaggi: Writing – original draft, Investigation, Data curation, Conceptualization. **Elisa Bannone:** Validation, Supervision, Formal analysis, Data curation. **Eugenia Melchiorre:** Resources, Investigation. **Michele Diana:** Writing – review & editing, Visualization, Validation, Supervision, Investigation. **Roberto Cotellese:** Visualization, Validation, Supervision, Investigation. **Gitana Maria Aceto:** Data curation, Formal analysis, Supervision.

Ethical approval statement

No ethical approval was needed since there was no involvement of patients.

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Declaration of competing interest

None declared.

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