

Commentary

Boosting pancreatic cancer chemotherapy by disrupting nerve–cancer crosstalk

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ABSTRACT

A preclinical study has developed a precision nano-intervention strategy targeting tumor-associated nerves to destroy nerve-fueled tumor growth in pancreatic cancer. In this strategy, *Escherichia coli* Nissle 1917-derived outer membrane vesicles (OMVs) are decorated with nerve-binding peptide for targeted delivery of co-loaded tropomyosin receptor kinase (Trk) inhibitors to tumor-associated nerves, thus precisely inhibiting nerve activity through the neurotrophin/Trk signaling pathway. Furthermore, the OMVs trigger M2-M1 switching, thus accelerating nerve injury. This nano-intervention strategy significantly enhances chemotherapy efficacy in pancreatic cancer.

Keywords: Cancer biology, Pharmaceuticals, Biochemistry

1. BACKGROUND

Pancreatic cancer, a highly aggressive solid malignancy with a poor prognosis, is characterized by perineural invasion—a distinct biological feature that markedly contributes to tumor progression and high recurrence rates [1–3]. Tropomyosin receptor kinase (Trk), a member of the neurotrophic tyrosine kinase receptor family, plays crucial roles in regulating synaptic strength and neural cell plasticity. Trk is overexpressed in the peripheral and central nervous system in the tumor environment, and its activation promotes tumor progression and metastasis [4]. Pancreatic cancer cells secrete nerve growth factor (NGF), which in turn binds and activates Trk receptors on nerve cells, thereby promoting nerve growth and facilitating tumor progression [1, 3]. Additionally, neural signaling can lead to the release of neurotransmitters promoting the growth and metastasis of tumor cells [5]. Sympathetic nerve activity can also promote tumor angiogenesis and provide nutrition to tumors [1, 5, 6]. The mutual communication and support between pancreatic cancer and nerves constitutes a crosstalk whose interruption may be a promising option for enhanced pancreatic cancer therapy. Encouragingly, targeting the interaction between pancreatic cancer

cells and the nervous system may provide a novel therapeutic strategy for this malignancy and other cancer types.

2. HIGHLIGHTS AND CRITICAL EVALUATION OF THE ORIGINAL STUDY

In *Nature Nanotechnology*, Qin et al. have reported the development of a nanocarrier system using engineered outer membrane vesicles (OMVs) derived from *Escherichia coli* Nissle 1917 (Figure 1) [7]. OMVs are a widely studied drug delivery system that can easily be decorated both inside the core and outside the membrane. In this study, the OMV-based nanocarriers incorporated a modified nerve-binding peptide NP41 on their surfaces for nerve-targeting while co-encapsulating the Trk inhibitor larotrectinib (Lar) inside. This nerve-targeting nanocarrier (Lar@NP-OMVs) effectively disrupts nerve–cancer crosstalk, suppresses neural activity, and modulates the tumor microenvironment, and therefore might serve as a promising therapeutic strategy for pancreatic cancer treatment. The multiple functions of Lar@NP-OMVs, with an all-in-one nanoarchitecture, were studied *in vitro* and *in vivo*.

2.1 In vitro neural targeting

To evaluate the neural targeting capability of the nanocomposites, the authors co-incubated DiD-labeled OMVs or NP-OMVs with rat pheochromocytoma PC12 cells, primary dorsal root ganglion neuronal cells, murine pancreatic cancer Panc02 cells, or human umbilical vein endothelial cells (HUVECs). As expected, modification with NP41 enhanced the neural targeting properties of the nanocomposites. This finding was corroborated in orthotopic Panc02 tumor-bearing mice, in which intravenously administered Lar@NP-OMVs resulted in the highest tumor accumulation of Lar and showed significant colocalization with neural markers.

2.2 In vitro inhibitory effects

To assess the inhibitory effects of Lar@NP-OMVs on the neurotrophic factor/Trk pathway, the authors observed the response of PC12 cells to NGF after treatment with Lar@NP-OMVs. Lar@NP-OMVs, because of enhanced internalization, significantly decreased neurite length and number, and effectively blocked nerve signal

conduction. Intriguingly, the supernatant of PC12 cells treated with Lar@NP-OMVs was deficient in neurotransmitters such as norepinephrine, and therefore might alleviate CD8⁺ T cell exhaustion and enhance their immune response [8]. When this supernatant was co-cultured with Panc02 cells, the cell viability and cell colony number significantly decreased. Therefore, by altering the secretion of neurotrophic factors, Lar@NP-OMVs appear to inhibit the proliferation and migration of pancreatic cancer cells. Consequently, Lar@NP-OMVs might provide a therapeutic strategy targeting nerve–cancer interactions. Additionally, nerve infiltration into tumors can increase the expression and secretion of various angiogenic factors in tumor cells via norepinephrine and epinephrine, thereby promoting tumor vascularization and growth [6]. The authors found that co-incubation of the supernatant from Lar@NP-OMV-treated PC12 cells with HUVECs significantly impaired the cells' angiogenic capacity. This effect was attributed to a decrease in norepinephrine levels in PC12 cells induced by Lar@NP-OMVs.

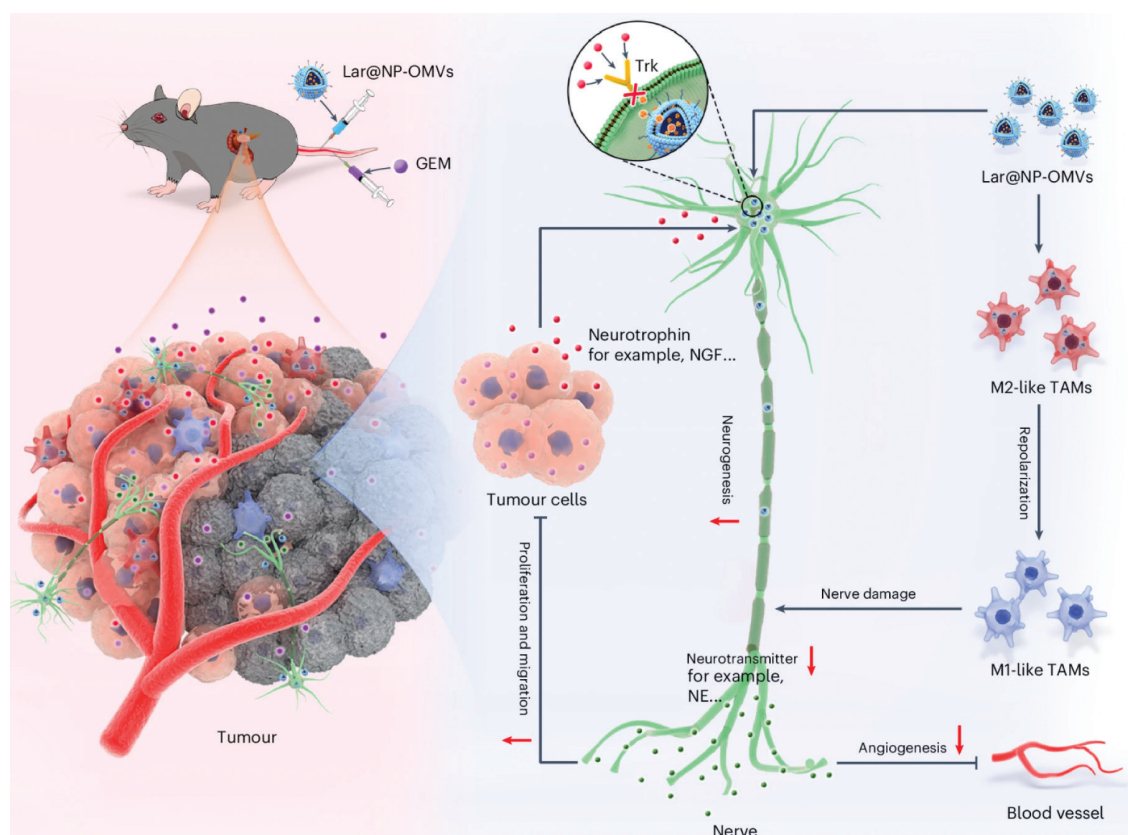


Figure 1 | Disrupting nerve–cancer interactions to boost pancreatic cancer chemotherapy.

Targeted disruption of nerve–cancer interactions via the *Escherichia coli*-derived Lar@NP-OMV platform reshapes the tumor microenvironment, impairs nerve function, and significantly enhances the antitumor efficacy of gemcitabine in preclinical pancreatic cancer models. Reproduced with permission from Ref. [7], Copyright © 2024, Springer Nature.

Commentary

2.3 Immune modulation

Extensive evidence indicates that perineural invasion by pancreatic cancer cells attracts migrating macrophages and induces their polarization to M2-like tumor-associated macrophages (TAMs) [9], which support nerve repair and promote the neural innervation of tumors. Given the abundance and plasticity of TAMs in the tumor microenvironment, reprogramming M2-like TAMs into pro-inflammatory M1-like TAMs is a promising immunotherapy strategy. *Escherichia coli*-derived OMVs contain various pathogen-associated molecular patterns, including lipopolysaccharides, flagellin, and peptidoglycan, which activate multiple Toll-like receptor signaling pathways and robustly stimulate innate immune responses [10]. The authors investigated the reprogramming potential of Lar@NP-OMVs in bone marrow-derived macrophages. The Lar@NP-OMVs effectively repolarized M2-like macrophages and significantly increased tumor necrosis factor secretion. This reprogramming impaired neural function through a paracrine mechanism, thereby decreasing neuronal survival, inducing apoptosis, and inhibiting neurite growth.

2.4 In vivo therapeutic effects

Injection of Lar@NP-OMVs into orthotopic pancreatic tumor-bearing mice demonstrated enhanced anticancer efficacy. Lar@NP-OMV treatment effectively repolarized M2-like TAMs, significantly decreased tumor nerve and blood vessel density, decreased nerve growth factor expression, reshaped the tumor microenvironment, and effectively inhibited nerve-mediated support of tumor growth. Chemotherapy is a common clinical treatment modality for pancreatic cancer; however, drug resistance can lead to poor outcomes [11]. One chemoresistance mechanism involves facilitation of sympathetic nerve activity by chemotherapy; for example, the frontline chemotherapeutic drug gemcitabine (GEM) promotes neurogenesis [12]. In this study, combining Lar@NP-OMVs with GEM further improved therapeutic efficacy, decreased peritoneal metastasis, and prolonged survival, thus highlighting the potential of Lar@NP-OMVs as adjuvants in chemotherapy to improve treatment outcomes across various cancer types.

Overall, the novel Lar@NP-OMV nanocarrier platform effectively disrupts nerve–tumor interactions in pancreatic cancer, inhibits neural activity, reshapes the tumor microenvironment, and exhibits synergistic effects with the chemotherapeutic agent GEM. This nanoplatform offers promising new insights for pancreatic cancer treatment and a potential strategic paradigm for broader cancer neurology applications: (1) nerve-driven tumor progression was highlighted in this study, and an engineering nanoplatform was designed to inhibit neurogenesis; (2) the nerve-intervention strategy led to chemotherapy sensitization in pancreatic cancer; (3)

other nanoplatform types (such as lipid nanoparticles, liposomes, and extracellular vesicles) may also be developed to increase therapeutic efficacy against pancreatic cancer.

3. TRANSLATIONAL IMPLICATIONS

In future clinical applications, considering potential neurotoxic effects due to the active targeting mediated by neural-targeting peptides will be crucial. Additional preclinical studies should carefully assess related adverse effects. Furthermore, under conditions, such as autoimmune neurological diseases (e.g., multiple sclerosis), that promote M1 macrophage activation and inflammation, the nanoplatform may benefit from enhanced tumor-specific targeting or selective activation within the tumor microenvironment to minimize off-target effects. In addition, evidence suggests that macrophages exposed to LPS can synthesize and release NGF [13], which may partially counteract the inhibitory effect of larotrectinib on Trk receptors. To precisely deliver Lar@NP-OMVs to tumor sites and counteract potential neurotoxicity, the following aspects may be considered: (1) dual-targeting strategies involving antibody-mediated targeting to tumors and nerves [14]; (2) local injection, such as minimally invasive interventional delivery; (3) OMV sources, e.g., collection of OMVs from attenuated bacteria; (4) surface modification with biomimetic coatings, such as cell membranes or biomineralization [15]; (5) regular monitoring for any signs of adverse effects and ability to respond promptly; and (6) use of alternative carriers, e.g., transformable carriers such as lipid nanoparticles. Notably, the intrinsic differences between mouse models and human pancreatic cancer pose further challenges. Mouse models of pancreatic cancer often do not fully recapitulate the complex tumor microenvironment in human pancreatic cancer, including immune cell infiltration and fibrotic remodeling [16]. Notably, the stromal composition in mouse models is relatively homogeneous, owing to the genetic similarity of stromal cells, which may obscure the heterogeneity and complexity of the human tumor stroma. More authentic experimental models (e.g., human organoid models or non-human primate models) are recommended to evaluate the pharmacokinetics and effects of this nanoplatform in patients. In summary, these potential limitations warrant further investigation to optimize the nanoplatform's composition and maximize therapeutic efficacy.

More importantly, the nano-intervention strategy in this work is universal, and therefore may also be appropriate for neuroendocrine tumors and other types of tumors with abundant infiltrated nerves, such as melanoma and glioblastoma. Additional efforts are required to elucidate the therapeutic efficacy of nerve-intervention strategies across tumor types.

4. PERSPECTIVES

Targeting the complex crosstalk among nerves, cancer cells, and the nerve–tumor microenvironment offers a promising new paradigm in cancer therapy. The sympathetic and sensory nervous systems have been shown to promote pancreatic cancer progression, whereas the parasympathetic nervous system may inhibit or suppress tumor initiation and growth [2, 5, 17]. Disrupting the balance between sympathetic and parasympathetic influences in pancreatic cancer might therefore be a valuable therapeutic approach. Because of tumor heterogeneity, and genetic and individual differences, the degree and nature of nerve–tumor crosstalk vary across tumors, thereby underscoring the need for further investigation of the molecular drivers of these interactions. Evolving techniques (e.g., transcriptomics, proteomics, metabolomics, and single-cell omics) can reveal the underlying molecular mechanisms. Additionally, organoid and 3D culture models offer experimental systems with enhanced physiological relevance by recapitulating cell–cell interactions and tissue architectures within the tumor microenvironment [18], thereby facilitating more accurate studies of nerve–tumor interactions. Moreover, substantially greater connective tissue hyperplasia is observed in human pancreatic tumors than in murine orthotopic models [19]. The dense fibrotic stroma in pancreatic cancer is composed of abundant tumor-associated fibroblasts, immunosuppressive cells, and diverse inflammation-driven extracellular matrix components. Decreasing fibroblast infiltration and activity is essential for overcoming treatment resistance and converting “cold” tumors into “hot” tumors. Further investigation of stromal remodeling mechanisms in pancreatic cancer is necessary to optimize treatment outcomes. To date, approaches antagonizing fibroblasts within the tumor microenvironment include differentiation blockade, depletion, phenotype switching, and inhibition of crosstalk between tumors and fibroblasts. Future studies are expected to explore the potential benefits of dual-intervention therapies targeting nerves and fibroblasts.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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