RESEARCH HIGHLIGHT

Neural crossroads of pancreatic cancer: how nociceptors drive tumor progression and immune evasion

Carmen Mota Reyes[1], Helmut Friess[1] and Ihsan Ekin Demir[1,2,3]✉

Cell Research (2025) 35:393–394; https://doi.org/10.1038/s41422-025-01124-5

Nociceptor neurons actively promote pancreatic ductal adenocarcinoma progression by suppressing immune responses through interactions with cancer-associated fibroblasts. Targeting their signaling pathways offers a novel strategy for enhancing anti-tumor immunity and managing cancer pain.

Among gastrointestinal malignancies, pancreatic ductal adenocarcinoma (PDAC) ranks among the most lethal due to its highly aggressive nature and resistance to conventional treatments.[1] A defining feature of PDAC is its pronounced neuropathy, characterized by hyperinnervation, neural hypertrophy, and perineural invasion, which have been linked to increased pain, heightened metastatic potential, and poorer patient survival.[2–4] While previous research has extensively examined autonomic innervation (sympathetic and parasympathetic) and its ability to either promote or suppress tumor growth depending on neuronal subtype, the role of nociceptor neurons remains largely underexplored.[5,6] Despite their well-established involvement in immune modulation during infections and autoimmune disorders, their impact on tumor progression has only recently gained recognition.[7]

Writing in *Cell Research*, Wang et al.[8] shed new light on the specific role of nociceptor neurons in shaping the PDAC tumor microenvironment (TME). Their study reveals that nociceptors not only exacerbate cancer pain but also promote tumor progression by interacting with cancer-associated fibroblasts (CAFs) and suppressing natural killer (NK) cell-mediated immune surveillance. Furthermore, inhibition of calcitonin gene-related peptide (CGRP) signaling emerges as a promising therapeutic avenue for targeting PDAC and associated cancer pain.

Their findings demonstrate that nociceptors engage in bidirectional communication with CAFs via CGRP and nerve growth factor (NGF) signaling. This interaction results in the downregulation of interleukin-15 expression in CAFs, leading to impaired NK infiltration and diminished cytotoxic function. NK cells play a crucial role in innate immunity, responsible for identifying and eliminating malignant cells.[9] Their suppression by CAFs has already been linked to enhanced tumor proliferation;[10] however, the authors describe a novel neural-driven mechanism underlying NK cell suppression, revealing an additional layer of regulation of tumor immune evasion.

A particularly promising aspect of this study is the potential therapeutic application of targeting nociceptor neurons. Wang et al. demonstrate that ablating nociceptors using resiniferatoxin, a high-affinity ligand for transient receptor potential vanilloid-1 (TRPV1), restored NK cell function leading to a significant reduction of tumor burden, pain alleviation, and improved survival in various PDAC mouse models. These findings align with prior research on melanoma, where ablation of $TRPV1^+$ neurons resulted in enhanced anti-tumor immunity, reduced tumor growth, and improved survival, largely through the elimination of CGRP's immunosuppressive effects on $CD8^+$ cytotoxic T cells.[11] Collectively, these results strengthen the rationale for targeting nociceptive neural circuits as a novel strategy for cancer treatment.

These findings have notable implications for both cancer therapy and pain management. One of the major barriers to effective PDAC treatment is its resistance to immunotherapy, largely due to its highly immunosuppressive TME. By identifying nociceptor neurons as key regulators of immune suppression in PDAC, the authors open new avenues for therapeutic intervention. Drugs modulating CGRP or NGF signaling, both of which are already targeted in clinical treatments for migraine and neuropathic pain in non-oncological settings, could potentially be repurposed to not only relieve cancer pain but also enhance anti-tumor immunity.

Despite these promising insights, the study has certain limitations. Most of the experimental findings in this study are based on murine models, and while correlative data from human PDAC patients support the conclusions, it remains uncertain whether targeting nociceptor–CAF interactions will yield similar therapeutic benefits in clinical settings. In addition, systemic nociceptor ablation may result in multiple side effects, given the role of these neurons in pain perception, gut motility, and other physiological functions.[12]

Beyond PDAC, this study highlights a broader principle in cancer neuroscience, the intricate interplay between the nervous system, the immune system, and the TME. While the traditional view of cancer progression has focused mainly on genetic mutations and dysregulated signaling within cancer cells themselves, it is becoming increasingly clear that tumors behave more like aberrant organs, hijacking multiple physiological systems to support their survival and spread. In this regard, the nervous system, with its complex signaling networks and extensive interactions with immune and stromal cells, represents a particularly compelling and underexploited therapeutic target.

[1]Department of Surgery, TUM University Hospital, Klinikum rechts der Isar, Munich, Germany. [2]Else Kröner Clinician Scientist Professor for Translational Pancreatic Surgery, Technical University of Munich, Munich, Germany. [3]Division of HPB Surgery, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey.
✉email: ekin.demir@tum.de

Published online: 7 May 2025

In conclusion, Wang et al. provide compelling evidence that nociceptor neurons are active participants in PDAC progression and immune modulation, rather than mere bystanders. Their study characterizes the immunomodulatory role of sensory neurons in cancer, demonstrating that targeting nociceptor–CAF interactions could reshape the immune landscape of PDAC. Moving forward, further research is needed to refine targeted neuromodulatory approaches, particularly in combination with immunotherapy, to unlock new treatment strategies for this so far untargetable disease.

REFERENCES

1. Jain, A. & Bhardwaj, V. *World J. Gastroenterol.* **27**, 6527–6550 (2021).
2. Ceyhan, G. O. et al. *Gastroenterology* **136**, 177–186.e1 (2009).
3. Demir, I. E. et al. *Cancers* **2**, 1513–1527 (2010).
4. Ceyhan, G. O. et al. *Am. J. Gastroenterol.* **104**, 2555–2565 (2009).
5. Saloman, J. L. et al. *Proc. Natl. Acad. Sci. USA* **113**, 3078–3083 (2016).
6. Renz, B. W. et al. *Cancer Discov.* **8**, 1458–1473 (2018).
7. Wu, M. et al. *Cell* **187**, 2935–2951.e19 (2024).
8. Wang, K. et al. *Cell Res.* **35**, 362–380 (2025).
9. Go, S. et al. *Elife* **13**, RP92672 (2024).
10. Kim, H. A. et al. *Cancer Cell Int.* **23**, 219 (2023).
11. Balood, M. et al. *Nature* **611**, 405–412 (2022).
12. Abdullah, N., Defaye, M. & Altier, C. *Am. J. Physiol. Gastrointest. Liver Physiol.* **319**, G718–G732 (2020).

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ihsan Ekin Demir.