Cell Research

www.nature.com/cr
www.cell-research.com

RESEARCH HIGHLIGHT

Nerves on tr[ac]k to support pancreatic cancer metabolism

Ruth A. White[1] and Timothy C. Wang[1]

Cell Research (2021) 31:381–382; https://doi.org/10.1038/s41422-020-00462-w

Nerve–cancer interactions modulate pancreatic cancer growth through direct effects on cancer cells and the microenvironment. New evidence now shows that nerves supply metabolic support to tumors by transporting amino acids to the nutrient-poor microenvironment.

Many studies have now shown that the nervous system plays an important role in the development and progression of numerous types of cancer, particularly pancreatic ductal adenocarcinoma (PDAC).[1–6] Similar in many ways to the effects of neoplasia on blood vessel growth and angiogenesis, pancreatic and other cancers modulate the neural microenvironment, promoting the outgrowth of axonal fibers towards the tumor and leading over time to a greater density and size of nerves within tumors.[7] While much of the early focus was on the findings of perineural invasion, with the invasion of nerve trunks by cancer, thus providing an additional pathway for spread, more recent reports have pointed to direct modulation of tumor growth by neural signaling.[1–4] Thus, there is a clear crosstalk between pancreatic tumors and the surrounding nerves, resulting in a remodeling of the neural microenvironment in a fashion more conducive to tumor growth.

Work from a number of laboratories has implicated the sympathetic and sensory nervous systems in the promotion of pancreatic cancer growth,[1,3] while the parasympathetic system appears to restrain or inhibit the progression of tumorigenesis in the pancreas.[4,8] In addition, these studies have clearly demonstrated the important role of specific neurotransmitters in this regulation; for example, epinephrine/norepinephrine and substance P promote growth through beta-2 adrenergic (Adrb2)[3] and neurokin-1 (NK-1) receptors,[6] respectively, and acetylcholine inhibits growth through muscarinic-1 (Chrm1) receptors.[4]

Nerves (and glia) have numerous functions beyond the simple release of neurotransmitters. In a recent publication in *Cell*, Banh et al.[9] make the remarkable observation that peripheral nerves support the growth and survival of PDAC by providing the conditionally essential amino acid, L-serine. Accumulating evidence suggests that PDAC tumors need multiple adaptive strategies to survive in the nutrient-poor, desmoplastic tumor microenvironment. Serine is required for numerous synthetic and metabolic pathways, and can be generated in mouse PDAC cells through the Serine Biosynthesis Pathway (SBP) but such synthetic capability is absent in up to 40% of human PDAC cells. The authors demonstrate that axons from DRG cells that comprise sensory and sympathetic neurons can release serine into nutrient-deprived environments, which can then support the growth of human PDAC cell lines that lack SBP enzymes and are dependent on exogenous serine for growth. Interestingly, serine turns out to be very important for mRNA translation. In the absence of serine, one observes a high rate of "ribosomal stalling", which occurs on two of the six serine codons (TCC and TCT). Thus, in the setting of serine deficiency, gene expression is selectively altered, shifting away from genes that contain TCC and TCT. The authors discovered that translation and secretion of Nerve Growth Factor (NGF) were enhanced upon serine deficiency and accompanied as previously shown by enhanced nerve infiltration. Moreover, the authors found that human SBP-deficient tumors expressed higher levels of NGF and were more highly innervated.

NGF has been previously implicated in pancreatic cancer. Renz and colleagues demonstrated that adrenergic signaling not only promotes the growth of Kras-mutant pancreatic cancer cells, but in combination with Kras signaling results in a significant upregulation of NGF and Brain-Derived Neurotrophic Factor (BDNF) by these cancer cells. The secretion of NGF by cancer cells induces further growth through autocrine effects by inducing the growth of nerve fibers and through its role in axonal guidance, drawing additional sympathetic fibers to the tumor. The actions of NGF are mediated through its receptor, TRK1, identifying two distinct strategies for the treatment of pancreatic cancer: Adrb2 blockade and TRK1 inhibition. Antagonism of Adrb2[3] and depletion of NGF[10] have shown efficacy in mouse models of PDAC. Banh et al. now show that TRK inhibition by an FDA-approved NGF/TRK inhibitor, LOXO-101, can reduce nervous innervation and decrease PDAC tumor burden in an orthotopic model.

Thus, this elegant study from the Kimmelman laboratory has significantly extended our understanding of nerve–cancer crosstalk towards now encompassing a role for nerves in the metabolic support of tumor cells. Given their long reach across moderate distances, nerves appear to be able to transport vital substances such as serine and glycine, from nutrient-rich areas to nutrient-poor areas. The finding reinforces the importance of nerves to the growth of neoplastic tissues and encourages further efforts at targeting therapeutically these interactions. Identification of such targets to modulate neural activity in tumors has led to the initiation of early-phase trials targeting the autonomic nervous system including muscarinic agonists (NCT03572283) and beta blockers (NCT02944201, NCT03838029 and NCT04245644). While this study further supports targeting the NGF/TRK interaction therapeutically (Fig. 1), one needs to keep in mind that neural outgrowth is governed by numerous other axonal guidance pathways that include both attractant and repellent signals, and thus there are likely other opportunities for neural modulation of tumor growth.

[1]Department of Medicine, Division of Digestive and Liver Diseases and Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, 1130 St. Nicholas Avenue, New York, NY 10032, USA
Correspondence: Timothy C. Wang (tcw21@columbia.edu)

Published online: 3 February 2021

© CEMCS, CAS 2021

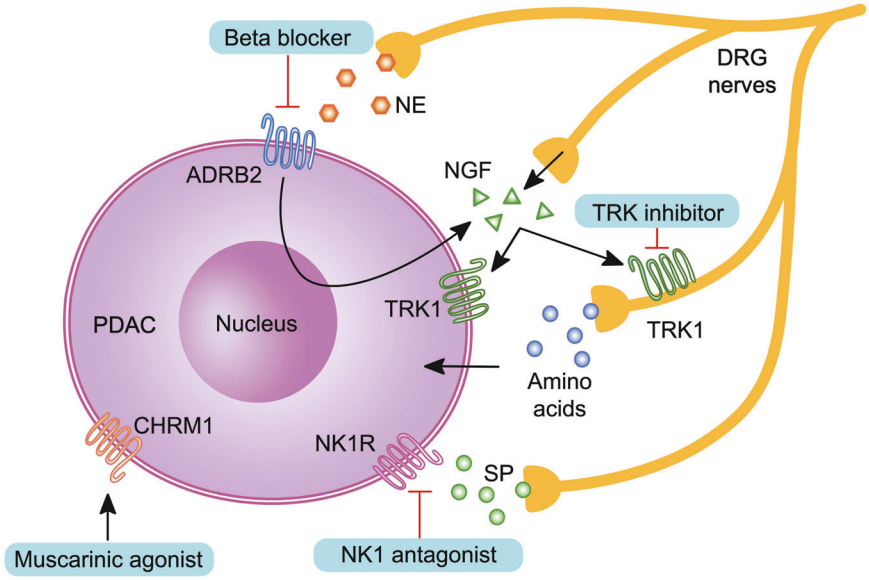

Fig. 1 Therapeutic strategies to modulate nerve–cancer crosstalk in PDAC. Modulation of nerve–cancer crosstalk is an emerging therapeutic strategy in the treatment of PDAC. NGF acts in both a cell-autonomous and non-cell-autonomous manner to stimulate tumor growth through direct effects on the tumor cell and by stimulating serine release from nerves to nutrient-poor environments. TRK1 can be inhibited by NGF/TRK inhibitor, which has been shown to inhibit PDAC growth in animal models. Inhibition of NK-1 on cancer cells inhibits PDAC xenograft growth and stimulation of muscarinic signaling through CHRM1 inhibits PDAC growth in animal models of PDAC by suppression of ERK/PI3K signaling.[4]

REFERENCES

1. Saloman, J. L. et al. *Proc. Natl. Acad. Sci. USA* **113**, 3078–3083 (2016).
2. Magnon, C. et al. *Science* **341**, 1236361 (2013).
3. Renz, B. W. et al. *Cancer Cell* **33**, 75–90 (2018).
4. Renz, B. W. et al. *Cancer Discov.* **8**, 1458–1473 (2018).
5. Zhao, C. M. et al. *Sci. Transl. Med.* **6**, 250ra115 (2014).
6. Sinha, S. et al. *Cancer Res.* **77**, 1868–1879 (2017).
7. Monje, M. et al. *Cell* **181**, 219–222 (2020).
8. Partecke, L. I. et al. *Oncotarget* **8**, 22501–22512 (2017).
9. Banh, R. S. et al. *Cell* **183**, 1202–1218 (2020).
10. Saloman, J. L. et al. *Pancreas* **47**, 856–863 (2018).