B-13

Dissecting the role of neuronal mimicry in pancreatic neuroendocrine tumours

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BACKGROUND

Pancreatic neuroendocrine tumours (PanNETs) are an understudied cancer type characterised by frequent metastasis, clinical recurrence, and high mortality rate. PanNETs originate from pancreatic islets, primarily β cells, and comprise two molecular subtypes: poorly invasive, relatively benign islet tumour (IT) and highly aggressive metastasis-like primary (MLP) tumour. The MLP subtype arises from IT through a switch in cell fate involving the acquisition of neuronal-like features, a process termed 'neuronal mimicry'. However, the precise role of this in PanNET progression and its underlying molecular mechanisms remain elusive. Here, we hypothesise that neuronal mimicry contributes to PanNET aggressiveness both through cancer cell-autonomous mechanisms and by promoting heterotypic interactions with tumour-infiltrating neurons.

METHODS

Bulk RNA sequencing data of tumours derived from PanNET patients and transgenic mouse models were analysed. Samples were scored for the enrichment of gene signatures associated with neuronal programs, proliferation, and invasion, and the correlation between these were determined. To examine heterotypic cancer-neuron interactions, multiplex immunofluorescence imaging with markers for cancer cells and neurons was performed on mouse model-derived tumours, in addition to in vitro co-culturing of PanNET cells with murine dorsal root ganglia (DRG).

RESULTS

Transcriptomic analyses of primary IT, primary MLP, and metastatic tumours revealed an upregulation of neuronal gene signatures during PanNET progression, coinciding with increased proliferative and invasive capacities. Quantitative immunofluorescence showed increased sympathetic innervation of the tumour core in advanced MLP lesions compared to IT. Finally, IT-like cancer cells undergo morphological changes resembling neurons, particularly development of neurites, when co-cultured with DRG. Interestingly, the neurites formed are more prominent with a higher DRG-to-cancer cell ratio in the co-culture, suggesting a dose-dependent effect.

CONCLUSIONS

Our results implicate neuronal mimicry as a potential driver of PanNET progression through both cancer cell-intrinsic and cell-extrinsic mechanisms. At the cell-extrinsic level, acquisition of neuronal-like features by cancer cells may potentiate crosstalk with neurons in the tumour microenvironment, in turn promoting tumour progression to more aggressive phenotypes.

Future experiments examining tumour innervation by different types of neurons at varying stages of disease progression will provide further mechanistic insight. At the cell-intrinsic level, activation of neuronal genes may directly confer cancer cells a growth advantage; this will be investigated further by genetic approaches, such as gain- and loss-of-function assays. The effect of pharmacologically disrupting cancer-neuron interactions will also be assessed, for instance using inhibitors of β-adrenergic receptors. Results from these studies may illuminate novel therapeutic avenues for PanNET by targeting neuronal gene programs and tumour innervation.

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