The neurotrophic factor neurturin contributes toward an aggressive cancer cell phenotype, neuropathic pain and neuronal plasticity in pancreatic cancer.

Abstract:
Neurotrophic factors possess an emerging role in the pathophysiology of several gastrointestinal disorders, regulating innervation, pain sensation and disease-associated neuroplasticity. Here, we aimed at characterizing the role of the neurotrophic factor neurturin (NRTN) and its receptor glial-cell-line-derived neurotrophic factor receptor alpha-2 (GFR?-2) in pancreatic cancer (PCa) and pancreatic neuropathy. For this purpose, NRTN and GFR?-2 were studied in normal human pancreas and PCa tissues via immunohistochemistry, quantitative reverse transcription-polymerase chain reaction, immunoblotting and correlated to abdominal pain. The impact of NRTN/GFR?-2 on PCa cell (PCC) biology was investigated via exposure to hypoxia, 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide viability and matrigel invasion assays in native and specific small interfering RNA-silenced PCCs. To assess the influence of NRTN on pancreatic neuroplasticity and neural invasion (NI), its impact was explored via an in vitro 'neuroplasticity assay' and a 3D neural migration assay. NRTN and GFR?-2 demonstrated a site-specific upregulation in PCa, predominantly in nerves, PCCs and extracellular matrix. Patients with severe pain demonstrated higher...
intraneural GFR?-2 immunoreactivity than patients with no pain. PCa tissue and PCCs contained increased amounts of NRTN, which was suppressed under hypoxia. NRTN promoted PCC invasiveness, and silencing of NRTN limited both PCC proliferation and invasion. Depletion of NRTN from PCa tissue extracts and PCC supernatants decreased axonal sprouting in neuronal cultures but did not influence glial density. Silencing of NRTN in PCCs boosted NI. We conclude that increased NRTN/GFR?-2 in PCa seems to promote an aggressive PCC phenotype and neuroplasticity in PCa. Accelerated NI following NRTN suppression constitutes a novel explanation for the attraction of PCC to nerves in the hypoxic PCa tumor microenvironment. PCa is characterized by intrapancreatic neuroplasticity and NI. Here, we show that PCC produce the neurotrophic factor NRTN, which reinforces their biological properties, triggers neuroplastic alterations, NI and influences pain sensation via the GFR?-2 receptor.