

## PS-1.8 Parasympathetic signaling suppresses pancreatic cancer development (W)

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**Zielsetzung:** The parasympathetic nervous system plays an important role in the regulation of epithelial homeostasis and has also been postulated to play a role in tumorigenesis. However, the exact role of the vagus nerve in pancreatic carcinogenesis is not well understood. Here we study the effects of muscarinic signaling on pancreatic tumorigenesis in a genetically engineered mouse model of pancreatic cancer (PDx1-Cre/KRasG12D (KC)).

**Methodik:** Mice were either vagotomized at 8 weeks or treated with a cholinergic agonist. Pancreatic tissue was collected and analyzed by immunohistochemistry and RT-PCR at 20 weeks of age; cells were isolated and assayed for colony and sphere forming assays. Different human (AsPC-1, BxPC-3, Mia PaCa-2, Panc-1) and murine (K-2548 and K-8282) pancreatic cancer cell lines were subjected to cholinergic and anti-cholinergic drugs and assayed by RT-PCR, Western blot and flow cytometry.

**Ergebnis:** In pancreatic organoid cultures derived from pancreata harboring an oncogenic KRas mutation, cholinergic agonists suppressed sphere formation significantly. Furthermore, pharmacological inhibition or genetic knockout of the muscarinic M3 receptor abolished this effect *in vitro*. In human and murine pancreatic cancer cells, anchorage independent growth and tumor sphere forming capacity were reduced by pretreatment with cholinergic agonists. Further evaluation revealed that parasympathetic agonists decrease the CD44+CD24+EpCAM+ cancer stem cell population in part via inhibition of the mTOR pathway. Vagotomy, when performed in KC mice at 8 weeks resulted in pancreatic cancer development in 20% of the animals at 20 week of age. . This was reproduced by in mice in which the M3 receptor was knock out was restricted to the pancreas (PDx1-Cre;KRasG12D;M3RF/F (KC-M3R)). On the other hand, treatment with the direct muscarinic agonist Bethanechol caused a deceleration of PanIN progression in KC mice.

**Schlussfolgerung:** Taken together, our findings suggest that vagal innervation has a regulatory role in pancreatic tumorigenesis via M3 receptor-mediated suppression of cancer stem cells. As each oncological resection of the pancreatic head is compulsorily associated with a parasympathetic denervation of the pancreas, and thereby a loss of its suppressive effect, this fact might partly explain the high local recurrence rate of this dismal disease. In order to overcome this problem an additional treatment with cholinergic drugs might be necessary.