Characterization of pancreatic glucagon-producing tumors and pituitary gland tumors in transgenic mice overexpressing MYCN in hGFAP-positive cells.

Amplification or overexpression of MYCN is involved in development and maintenance of multiple malignancies. A subset of these tumors originates from neural precursors, including the most aggressive forms of the childhood tumors, neuroblastoma and medulloblastoma. In order to model the spectrum of MYCN-driven neoplasms in mice, we transgenically overexpressed MYCN under the control of the human GFAP-promoter that, among other targets, drives expression in neural progenitor cells. However, LSL-MYCN; hGFAP-Cre double transgenic mice did neither develop neural crest tumors nor tumors of the central nervous system, but presented with neuroendocrine tumors of the pancreas and, less frequently, the pituitary gland. Pituitary tumors expressed chromogranin A and closely resembled human pituitary adenomas. Pancreatic tumors strongly produced and secreted glucagon, suggesting that they derived from glucagon- and GFAP-positive islet cells. Interestingly, 3 out of 9 human pancreatic neuroendocrine tumors expressed MYCN, supporting the similarity of the mouse tumors to the
Serial transplantations of mouse tumor cells into immunocompromised mice confirmed their fully transformed phenotype. MYCN-directed treatment by AuroraA- or Brd4-inhibitors resulted in significantly decreased cell proliferation in vitro and reduced tumor growth in vivo. In summary, we provide a novel mouse model for neuroendocrine tumors of the pancreas and pituitary gland that is dependent on MYCN expression and that may help to evaluate MYCN-directed therapies.