B-Raf is required for ERK activation and tumor progression in a mouse model of pancreatic beta-cell carcinogenesis

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Activation of the Raf/MEK/ERK pathway, often by gain-of-function mutations of RAS or RAF, is observed in many human cancers. The extracellular signal-regulated kinase (ERK) pathway is required for the proliferation of cancer cell lines harboring activating BRAF or, to a lesser extent, activating RAS mutations. It is still unclear, however, whether the pathway is required in vivo for tumor development, particularly in tumors in which B-Raf is not mutationally activated. During embryonic development, B-Raf is essential for angiogenesis in the placenta. To address the question of whether B-Raf contributed to tumor angiogenesis in vivo we conditionally ablated B-Raf in a model of pancreatic islet carcinoma driven by the functional inactivation of tumor suppressors (RIP1Tag2), which critically depends on angiogenesis for growth. We find that B-Raf is dispensable for the proliferation of tumor cells in culture, but necessary for ERK activation and for the expression of angiogenic factors by tumor cells in vivo and in vitro. In vivo, these defects result in the formation of hollow tumors with decreased vessel density and strongly reduced proliferation. The progression from adenoma to carcinoma is also significantly impaired. Thus, endogenous B-Raf contributes to the development of RIP1Tag2 tumors by supporting the stromal response and tumor progression.
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