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The MAP Kinase-activated Protein Kinase 2 Promotes the Development and Progression of Pancreatic Neuroendocrine Tumors Involving Action Mediated by Macrophages

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BACKGROUND: Accumulating evidence highlights the significance of immune response in the development and progression of pancreatic neuroendocrine tumors (PNETs). The MAP kinase-activated protein kinase 2 (MK2) is a crucial regulator of numerous processes including cell division and differentiation and is an important mediator of inflammation. The aim of our study was to determinate the contribution of signaling mediated by MK2 in the development and progression of PNETs.

METHODS: MK2 inhibitors were administrated for five weeks to the rat insulin promoter 1 driven viral SV40 large T antigen (RipTag2) transgenic mice. PNETs from RipTag2 mice were obtained, weighted and dissected into 8 mg pieces, incubated in complete RPMI medium for 18 h and supernatants were analyzed for cytokines and chemokines by multiplex array. Tumor killing assays were performed using PNET cells derived from untreated RipTag2 mice and activated wild type or MK2-/- bone marrow-derived macrophages. Cells were incubated for 24 h and stained with F4/80 and annexin V, and analyzed by flow cytometry.

RESULTS: In the RipTag2 transgenic mice model of PNETs, inhibition of MK2 led to significant reduction of tumor weight and was related to improvement of survival time. Ex vivo analysis of PNETs obtained from RipTag2 mice revealed that MK2 inhibition prevented secretion of cytokines and chemokines related to macrophage function. Finally, MK2-/- macrophages showed increased tumor cell killing by annexin V analysis.

CONCLUSION: The results indicated that MK2 inhibition suppresses the

development and progression of PNETs and these phenomena seems to be associated with anti-tumorigenic macrophage response.

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