RSUME is implicated in tumorigenesis and metastasis of pancreatic neuroendocrine tumors.

Abstract:

The factors triggering pancreatic neuroendocrine tumor (PanNET) progression are largely unknown. Here we investigated the role and mechanisms of the sumoylation enhancing protein RSUME in PanNET tumorigenesis. Immunohistochemical studies showed that RSUME is strongly expressed in normal human pancreas, in particular in ?-cells. RSUME expression is reduced in insulinomas and is nearly absent in other types of PanNETs suggesting a role in PanNET tumorigenesis. In human pancreatic neuroendocrine BON1 cells, RSUME stimulates hypoxia-inducible factor-1? (HIF-1?) and vascular endothelial growth factor-A (VEGF-A), which are key components of tumor neovascularisation. In contrast, RSUME suppresses nuclear factor-?B (NF-?B) and its target interleukin-8 (IL-8). Correspondingly, PanNET cells with RSUME knockdown showed decreased HIF-1? activity and increased NF-?B and IL-8 production leading to a moderate reduction of VEGF-A release as reduced HIF-1?/VEGF-A production is partly compensated by NF-?B/IL-8-induced VEGF-A. Notably, RSUME stabilizes the tumor suppressor PTEN, which is frequently lost in PanNETs and whose absence is associated with metastasis formation. In vivo orthotopic
transplantation of PanNET cells with or without RSUME expression into nude mice showed that PanNETs without RSUME have reduced PTEN expression, grow faster and form multiple liver metastases. In sum, RSUME differentially regulates key components of PanNET formation suggesting that the observed loss of RSUME in advanced PanNETs is critically involved in PanNET tumorigenesis, particularly in metastasis formation.