RSUME regulates tumorigenesis and metastasis in pancreatic neuroendocrine tumors

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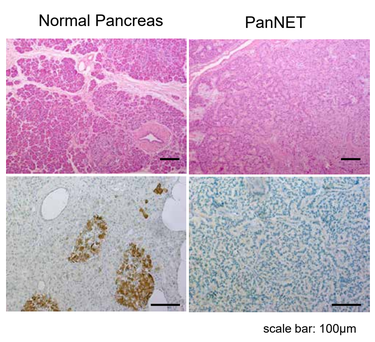
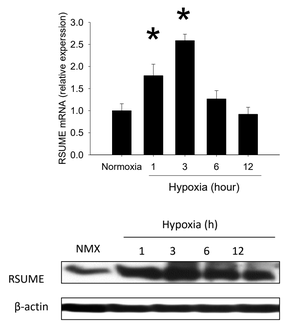
INTRODUCTION: Pancreatic neuroendocrine tumors are rare and represent only about 1 to 2% of all neoplasias of the pancreas . They derive from hormone producing cells of the pancreas and are correspondingly designated as insulinomas, gastrinomas, VIPomas, glucogoninomas etc. The pathogenesis of this heterogenous family of tumors is largely unknown. RSUME was previously identified as sumoylation enhancer protein to stablize target genes such as HIF1a and IκBα. We found that RSUME is highly expressed in pancreas but loss of expression in PanNETs. Therefore the (patho-) physiological consequence due to RSUME absence was studied using PanNET derived BON1 cells. We found that RSUME knockdown in BON cells led to decrease HIF1α expression and vascular density and increased the liver metastasis tested in an orthotopic tumor model and the molecular mechanisms are partly attribute to decreased PTEN expression and increased NFκB activity.

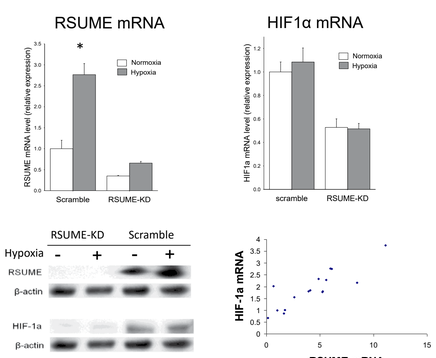
1 RSUME is down-regulated in PanNETs and regulates VEGF through HIF1α in PanNET cells



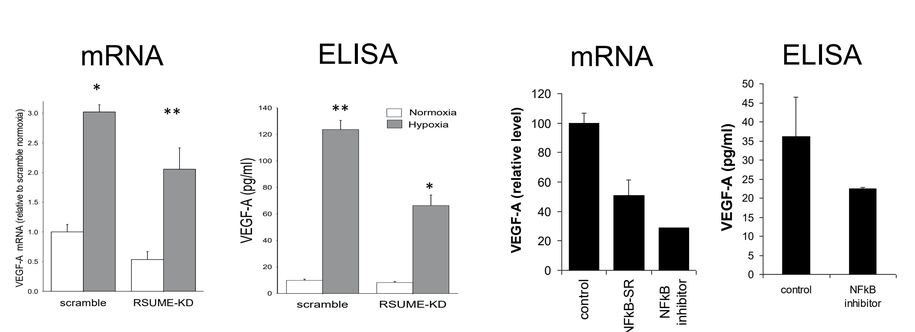
RSUME is downregualted in PanNETs



RSUME is induced during hypoxia



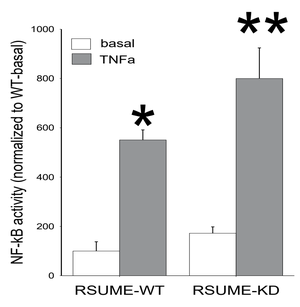
RSUME positively regulates HIF1α expression



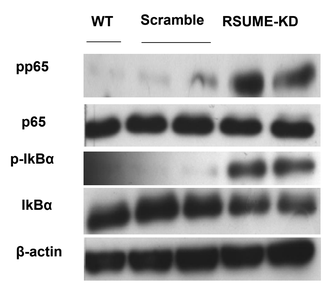
VEGF-A is decreased in RSUME KD cells

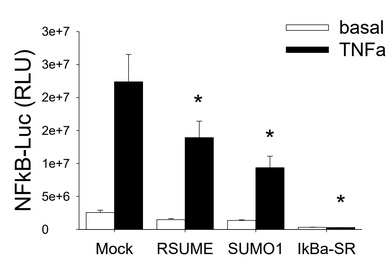
NFκB regulates VEGF-A

2 RSUME negatively regulates NF-κB activity by enhancing IκBα SUMOylation

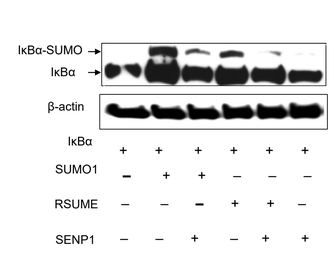


NFkB activity is increased in RSUME knockdown BON1 cells

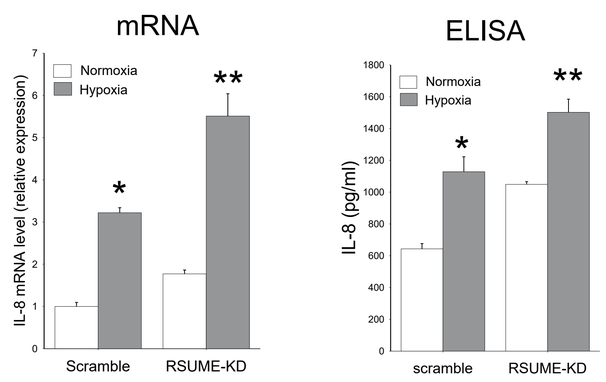




RSUME overexpression inhibits NFκB

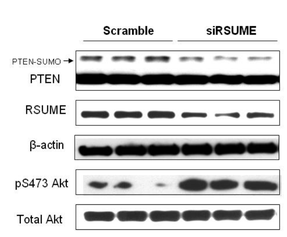


RSUME enhances IκBα sumoylation



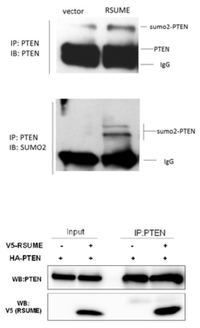
IL8 level is increased in RSUME knockdown BON1 cells

3 RSUME enhances PTEN sumoylation, protein stability and increases its nucleus accumulation



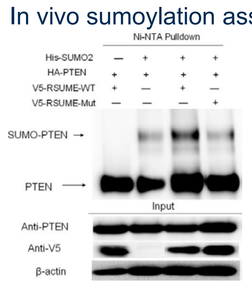
RSUME KD reduces PTEN

Co-IP experiment

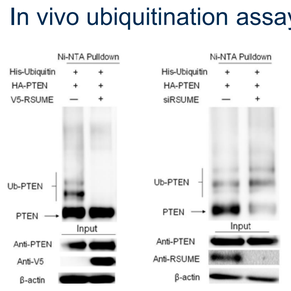


RSUME and PTEN interacts

In vivo sumoylation assay



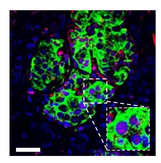
In vivo ubiquitination assay



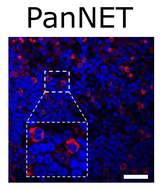
RSUME enhances PTEN sumoylation and decreases ubiquitination and increase protein stability

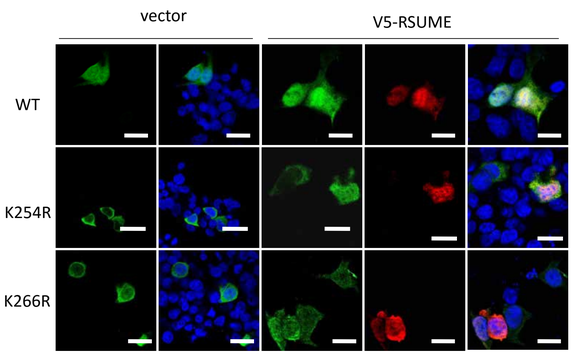
Protein degradation assay

pancreas



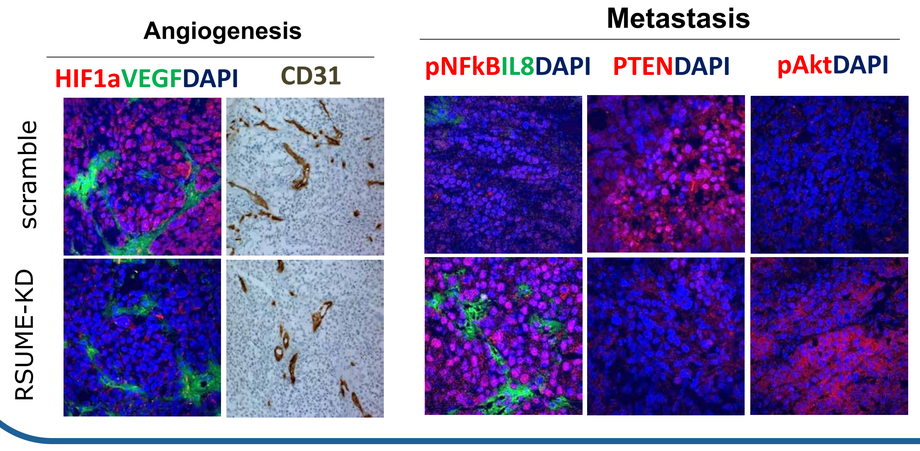
PanNET



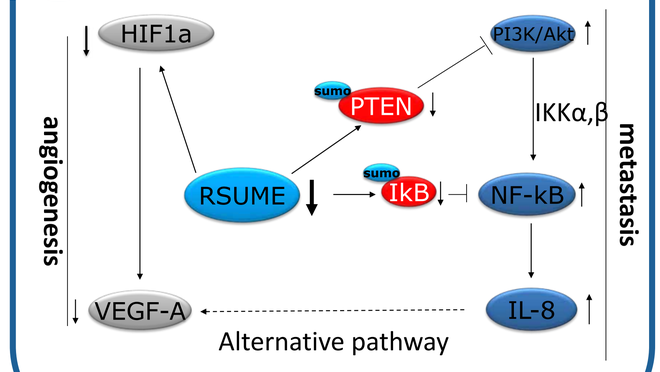


RSUME increases PTEN nucleus accumulation

4 RSUME knockdown increases metastasis in vivo



5 model



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