Akt dysregulation by loss of *PHLDA3* is an important determinant of pancreatic neuroendocrine tumor progression

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Pancreatic neuroendocrine tumors (PanNETs) are rare cancers derived from pancreatic islets. We previously have identified PHLDA3 as a repressor of Akt and a novel tumor suppressor of PanNETs. We also have demonstrated that functional loss of PHLDA3 correlates with the malignant progression of human PanNETs. To further analyze the effects of *PHLDA3* deficiency on PanNET progression, we have crossed the *PHLDA3*-deficient mice with another mouse model that develops low-grade PanNETs. By analyzing these mice, we found that loss of *PHLDA3* induced aberrant Akt activation in islet cells and resulted in an early formation of malignant PanNETs. Akt dysregulation affects cell differentiation and metabolism. We found that the malignant PanNETs observed in these mice were accompanied by reduced hormone production and abnormal cell differentiation. We are currently analyzing the functional changes of several key regulators of differentiation and metabolism to identify the decisive pathways for PanNET progression. Our findings will reveal the importance of PHLDA3 function in PanNET progression and provide novel therapies to treat PanNETs through targeting the PHLDA3/Akt-mediated signaling pathways.

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PHLDA3-Akt ネットワークによる膵神経内分泌腫瘍悪性化の制御

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