（様式4）（Form4）

学 位 論 文 の 内 容 の 要 旨

Dissertation Abstract

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（学位論文のタイトル） Title

Identification of *Ppy*-lineage cells as a novel origin of pancreatic ductal adenocarcinoma

（膵管腺癌の新規発生源としての*Ppy*系細胞の同定）

（論文目録（様式3）」の主論文の部分を記載する。英文の場合は和訳をつける）

（学位論文の要旨）2,000字程度、A4判 （approx. 800 Words in English /A4 size）

The *Ppy*-gene encodes the pancreatic polypeptide (PP) secreted by PP- or γ- cells, a subtype of endocrine cells in the islets' periphery. For a detailed characterization of PP-cells, we aimed to establish PP-cell lines. To this end, we generated a mouse model which harbors the *SV40 large T* antigen (*TAg*) in the Rosa26 locus, which is expressed upon *Ppy*-promoter mediated *Cre-loxP* recombination. While *Insulin1-Cre* mediated *TAg* expression in beta cells resulted in insulinoma, *Ppy-Cre* mediated *TAg* expression resulted in malignant transformation of *Ppy*-lineage cells. Mice showed distorted islet structural integrity at 5-days old compared with normal islets. $CK19^{+}$ duct-like lesions contiguous from the islets were observed at 2-weeks old, and aggressive pancreatic ductal adenocarcinoma (PDAC) at 4-weeks old, suggesting that PDAC can originate from the islet/endocrine pancreas, which was rather unexpected as PDAC is generally believed to originate from the exocrine pancreas. RNA-seq analysis of *Ppy*-lineage islet cells from 7-day-old TAg^{+} mice showed a downregulation and upregulation of endocrine and exocrine genes, respectively, in addition to the upregulation of genes and pathways associated with PDAC. These results suggest that the expression of an oncogene in *Ppy*-lineage cells induces a switch from endocrine cell fate to PDAC. Our findings demonstrate that *Ppy*-lineage cells may be an origin of PDAC and provide novel insights into the pathogenesis of and possible therapeutic

strategies for pancreatic cancer.