Mitochondrial anti-fission signaling elicited by the β isoform of PI3K suggests a treatment strategy for KRAS-driven cancers

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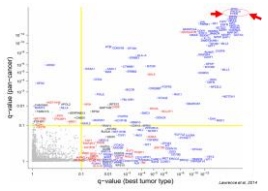
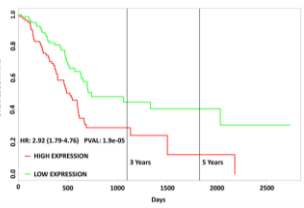
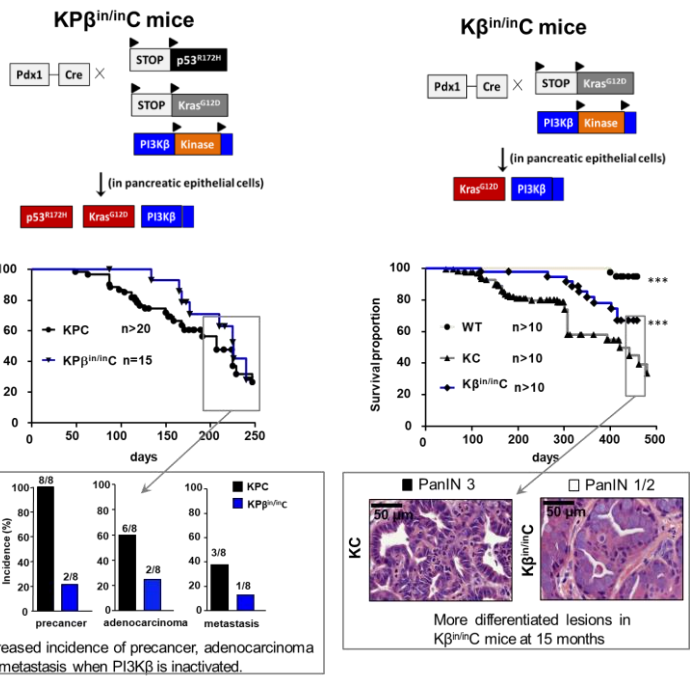
Introduction

Oncogenic KRAS mutations are the main cancer genomic event which lead to hyperactivation of the class I PI3K pathway in tumors. In pancreatic cancer (PDAC) where KRAS G12 mutations are very frequent, we found that mutant KRAS increased expression of 3 out 4 class I PI3Ks, including the PI3Kβ for which the role in KRAS oncogenic signaling is unknown.



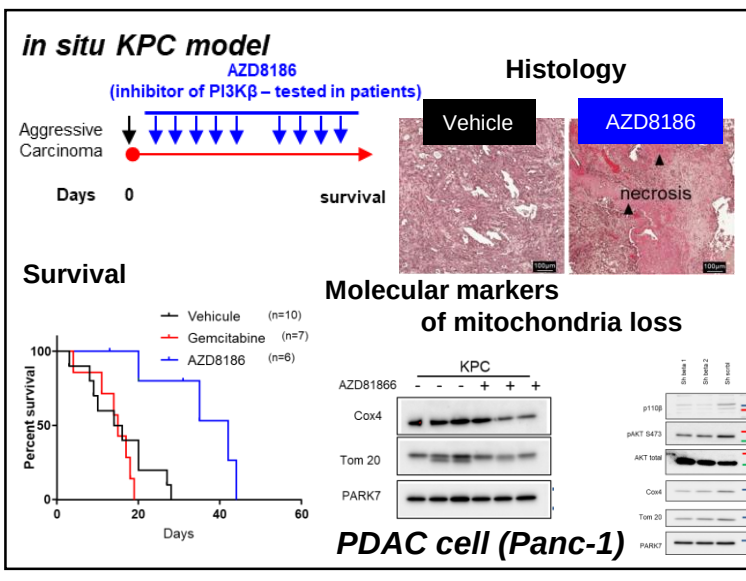


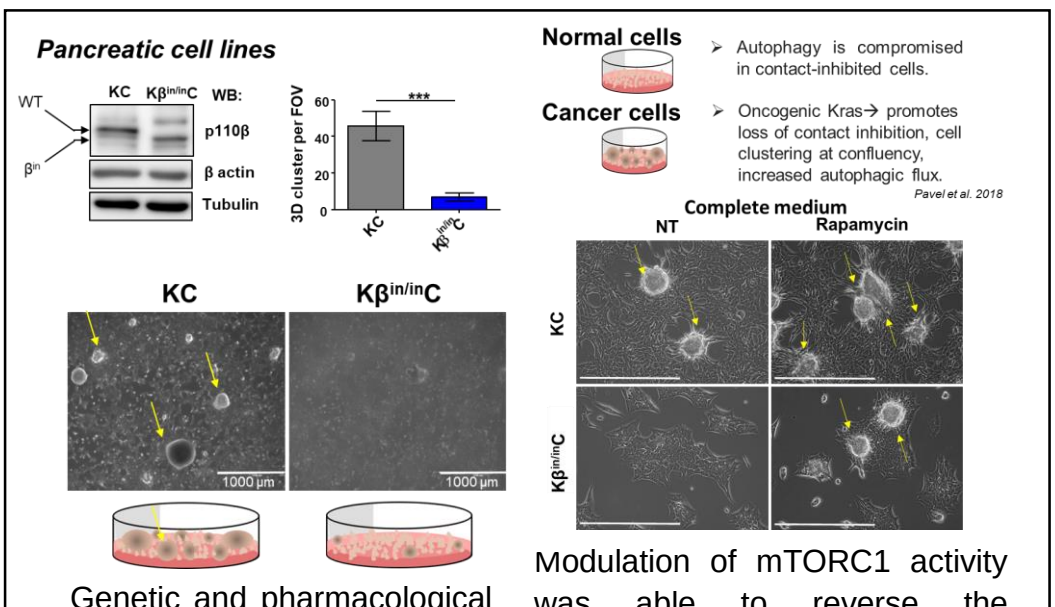
PDAC patients (90% with mutant KRAS) with increased PI3Kβ expression presented a bad prognosis.



Decreased incidence of precancer, adenocarcinoma and metastasis when PI3Kβ is inactivated.

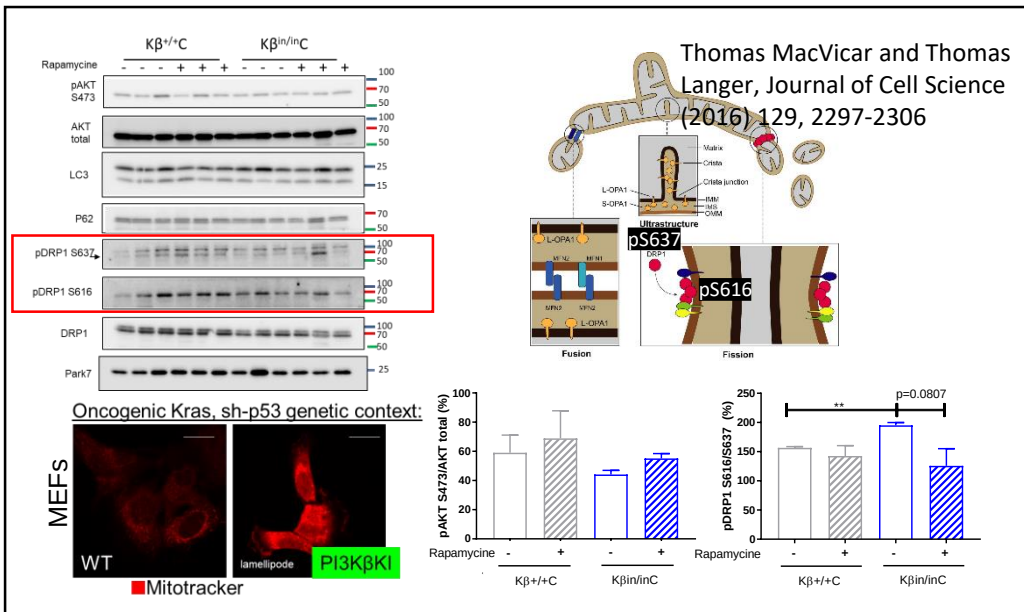
Mice with PI3Kβ activity-deficient pancreatic cells presented increased survival to oncogenic KRAS-induced carcinogenesis in combination or not with mutant p53.



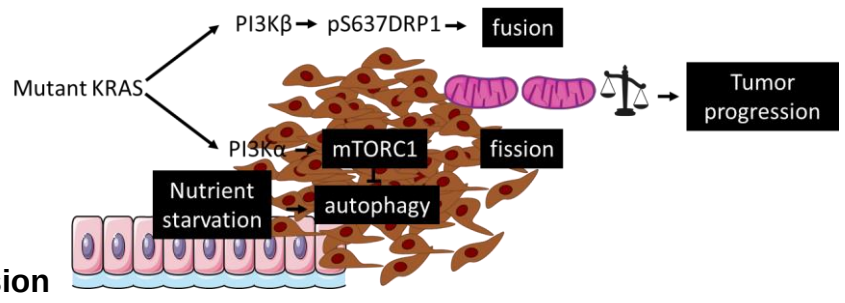


Genetic and pharmacological inactivation of PI3Kβ decreased the loss of cell-cell contact inhibition.

Modulation of mTORC1 activity was able to reverse the protective phenotype induced by PI3Kβ inactivation *in vitro and in vivo (not shown)*.



Inactivation of PI3Kβ led to increased pro-fission signaling.
Modulation of mTORC1 activity was able to reverse the induction of increased pS616/pS637 DRP1 ratio leading to fission signalling.



Conclusion

PI3Kβ contributes to cancer progression in oncogenic KRAS context by promoting mitochondrial fusion signaling under stress.
PI3Kβ is a significant target for cancer treatment.

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