# AB002. S002. Wild-type *KRAS* allele exerts its tumor-suppressive function through decreased Yap1 activation in pancreatic cancer

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**Abstract:** *KRAS* is the most frequently mutated oncogene (about 95%) in pancreatic ductal adenocarcinoma (PDAC) and it has been shown to be essential for pancreatic tumor initiation and maintenance in both humans and mice. We have previously reported that the wild-type *KRAS* allele was selectively lost in both primary pancreatic tumors and metastases developed in a mouse model of PDAC, and the frequency of the wild-type loss increased from primary tumors to metastases in this mouse model and human pancreatic cancer cells. To interrogate the wild-type *KRAS* functions and its underlying mechanisms in pancreatic tumorigenesis, we restored the wild-type *KRAS* allele in a doxycycline (Dox) inducible manner in two pancreatic cancer cell lines that have undergone loss of the wild-type allele. We observed that the re-expression of the wild-type *KRAS* significantly reverse the proliferation, motility, and colony formation capabilities of these cancer cells *in vitro*. Furthermore, *in vivo* xenograft studies also demonstrated stalled tumor growth upon wild-type *KRAS* restoration. In contrast, overexpression of wild-type *KRAS* exerted no impact on pancreatic cancer cells that have retained the wild-type *KRAS* allele, suggesting that it's the presence of the wild-type *KRAS* allele, not the dosage of total *KRAS* or the ratio of wild-type and mutant *KRAS*, that is vital in regulating tumor growth and metastasis. Lastly we examined several downstream signaling pathways associated with the regulation of *KRAS* and observed decreased Yap1 expression and nuclear translocation were induced by the restoration of the wild-type *KRAS* allele. Together these results ascribe the wild-type *KRAS* allele a tumor-suppressive role in the context of the mutant KRAS allele in pancreatic tumorigenesis via the inhibition of Yap1 activation.

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