B6-*Kras*$^{LSL-G12D}$

Stain Name：B6/JGpt-*Kras*$^{em1Cin(loxP-SA-stop-SD-loxP-G12D)}$/Gpt

Strain Type：Targeted Mutation

Strain Number：T004551

Background：C57BL/6JGpt

Description

KRAS(KRAS Proto-Oncogene, GTPase) is a membrane-associated GTPase signaling protein that regulates proliferation, differentiation, and cell survival[1]. Missense mutations at codons 12, 13, and 61 lock the protein in its GTP-bound form thus permitting its constitutive interaction with and activation of multiple effectors[2], which promoting effects on cell proliferation and cell survival. Mutations of KRAS are found in a variety of human malignancies, including in pancreatic cancer, colorectal cancer, and non-small cell lung cancer at high frequency. However, no direct RAS inhibitors exist for cancer therapy.

To study the relationship between the mutational activation of KRAS and tumorigenesis, we established B6-Loxp-Stop-Loxp *Kras* G12D (B6-*Kras*$^{LSL-G12D}$) strain. Floxed Stop sequences will be deleted in the mouse genome when Cre recombinase exists, oncogenic KRAS G12D protein are expressed with endogenous levels following removal of the stop cassette, which allows to control of the timing, location, and the multiplicity of tumor initiation. When B6-*Kras*$^{LSL-G12D}$ mice crossed with B6-*Lyz2* Cre mice(expressing Cre recombinase in myeloid cell lineage and lung), the offspring mice were developed lung tumor with inflammatory cell infiltration at 6 weeks age. When B6-*Kras*$^{LSL-G12D}$ mice crossed with B6-*Alb* Cre mice (expressing Cre recombinase in liver and lung), the offspring mice (at 36 weeks age) were developed hepatobiliary cancer and the whole liver was covered with tumor tissue. B6-*Kras*$^{LSL-G12D}$ mice model can be used to study the occurrence and development of cancer.

Strategy

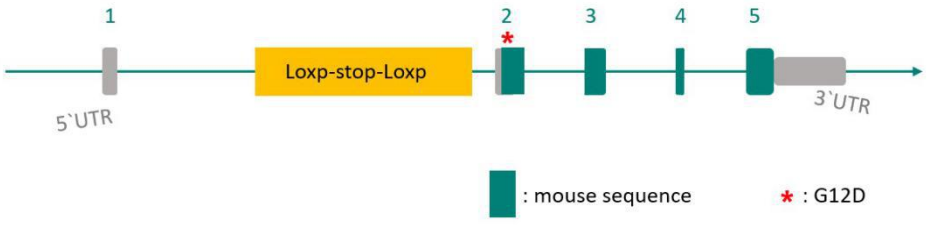

Fig.1 Schematic diagram of B6-*Kras*$^{LSL-G12D}$ model stratery.

Application

1. Pancreatic cancer, colorectal cancer, and non-small cell lung cancer study
2. Screen of small-molecule antitumor drugs

Data support

1. After B6-*Kras*$^{LSL\text{-}G12D}$ mice removal of stop cassette were experssed G12D successfully and developed tumor

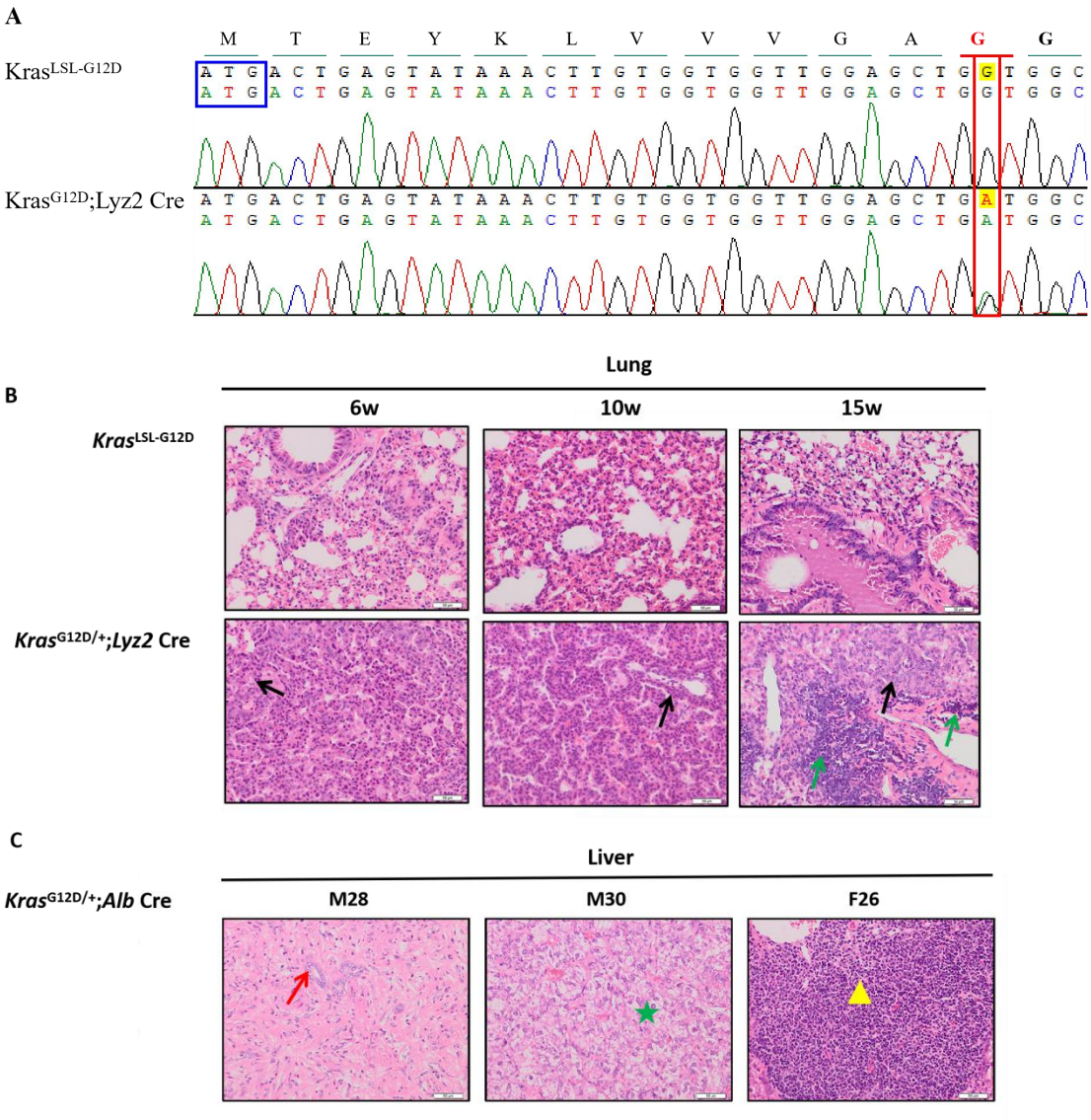

Fig2. Histopathology and mRNA expression analysis of B6-*Kras*$^{LSL\text{-}G12D}$ mice. Fig.2A,B:

B6-*Kras*$^{LSL-G12D}$ mice crossed with B6-*Lyz2* Cre mice, the lung of offspring mice(B6-*Kras* $^{G12D/+}$*;Lyz2* Cre) at 6 weeks, 10weeks, 15 weeks age were extracted total mRNA for Kras G12D mRNA expression analysis and a part of lung tissue was examined by HE staining for pathology analysis.**The results showed that:** The codon 12 mutated from GGT to GAT and KRAS G12D protents were expressed following the removal of stop cassette within lung of *Kras*$^{G12D/+}$; *Lyz2* Cre mice(Fig.2A). Further more, *Kras*$^{G12D/+}$; *Lyz2* Cre mice at 6 weeks age were developed lung cancer with multiple lesions and inflammatory cell infiltration(Fig.2B)

Fig.2C: B6-*Kras*$^{LSL-G12D}$ mice crossed with B6-*Alb* Cre mice, the liver of offspring mice(B6-*Kras* $^{G12D/+}$*;Alb* Cre) were examined at 36 weeks age by HE staining for pathology analysis. **The results showed that:** *Kras*$^{G12D/+}$; *Alb* Cre mice at 36 weeks age were developed hepatobiliary cancer and the whole liver is covered with tumor tissue.

(Note:200x, bar=50μm. Red and black arrow: tumor cells line up as glandular tubes ; green arrow: inflammatory cell infiltration; green star: Cytoplasmic looseness in lumpy lesions;yellow star: mass of tumor cells can be seen in the vein area).

Take togather： KRAS G12D proteins are expressed following the removal of stop cassette, B6-*Kras*$^{LSL-G12D}$ mice can be used to study the occurrence and development of cancer.

References

1. Campbell, Sharon L., et al. "Increasing complexity of Ras signaling." *Oncogene* 17.11 (1998): 1395.

2. Downward, Julian. "Targeting RAS signalling pathways in cancer therapy." *Nature Reviews Cancer* 3.1 (2003): 11.