KS

Strain Name： B6/JGpt-*Kras*$^{FLEX-G12C}$; *Sftpc*$^{em1Cin(IRES-iCre)}$/Gpt

Strain Type： Knock-in

Strain Number： T057162

Background： C57BL/6JGpt

Description

KRAS (Kirsten rat sarcoma virus) is a membrane-associated GTPase signaling protein that participates in the process of cell proliferation and differentiation [1]. Somatic mutations in the KRAS gene are involved in the development of several types of cancer, particularly pancreatic, colorectal cancers, and lung cancers. The mutation on codon 12, which is particularly prevalent in pancreatic cancers, substitutes glycine for valine or aspartate [2] and leads to GTPase losing its function and essentially allows GTP to continue to signal cell growth [3], thereby allowing uncontrolled and continuous growth, angiogenesis as well as overriding apoptosis [1]. Although it has long been deemed “undruggable”, with the development of drugs specifically binding the KRAS-G12C mutant protein, clinical trials that directly inhibit oncogenic RAS have recently made promising improvements.

Surfactant protein C (SP-C), is one of the pulmonary surfactant proteins, encoded by the SFTPC gene. IRES-iCre was introduced downstream of the 3’UTR of mouse Sftpc gene by CRISPR/Cas9 technology to build the Sftpc-IRES-iCre(T004715) mice [3]. When crossed with a strain with a loxP site flanked sequence in its genome, Cre-mediated recombination will result in the excision of the DNA fragment between the two loxPs in Type II alveolar cells.

To study the relationship between the mutational activation of KRAS and tumorigenesis, and promote the development of KRAS-G12C inhibitors, we established Kras$^{FLEX-G12C}$ strain. When Kras$^{FLEX-G12C}$ mice crossed with Sftpc-IRES-iCre mice, floxed sequences are likely to reverse and delete in the Kras$^{FLEX-G12C}$ mouse genome. The offspring mice developed the lung tumor. Kras$^{FLEX-G12C}$ mouse model can be used to study the occurrence and development of lung cancer.

Strategy

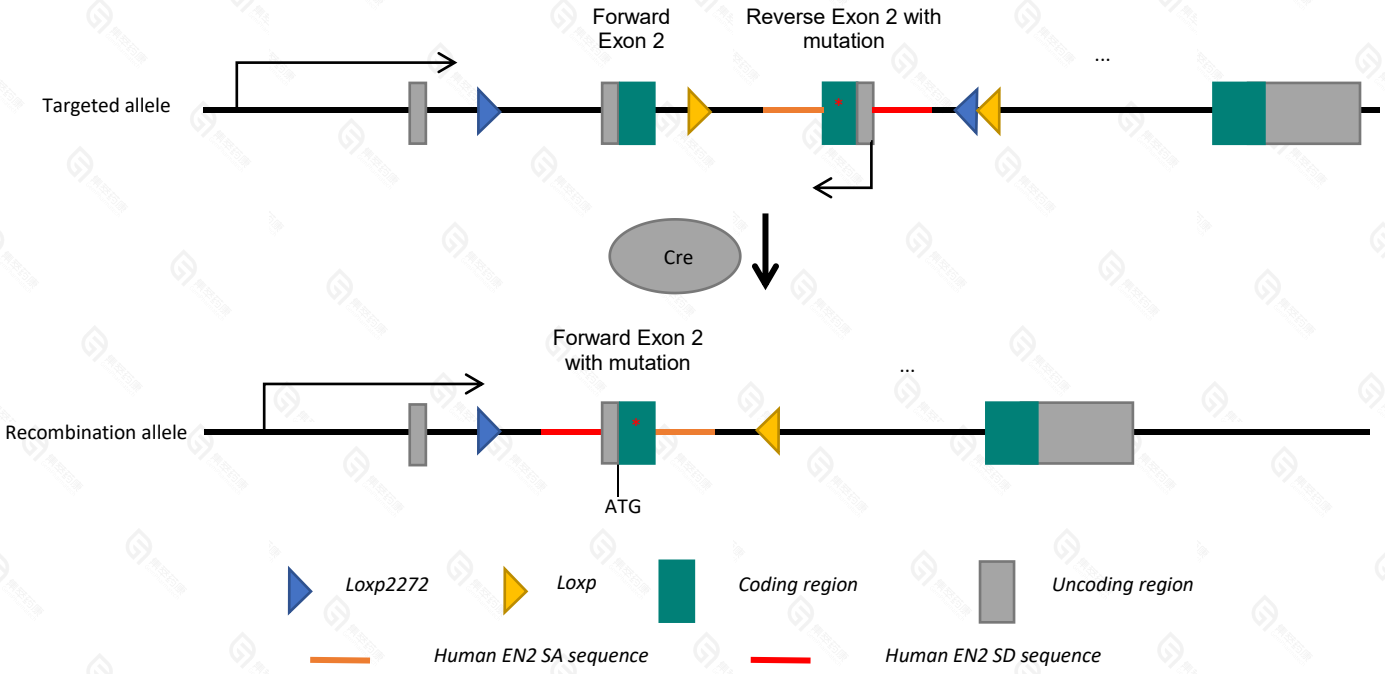

Fig 1. Schematic diagram of Kras$^{FLEX-G12C}$ model stratery

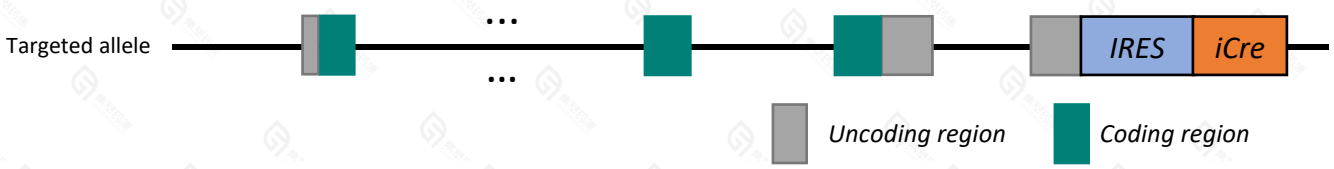

Fig 2. Schematic diagram of Sftpc-IRES-iCre model stratery

Applications

1. Non-small cell lung cancer study
2. Screen of small-molecule antitumor drugs

Supporting data

1. Histopathology data

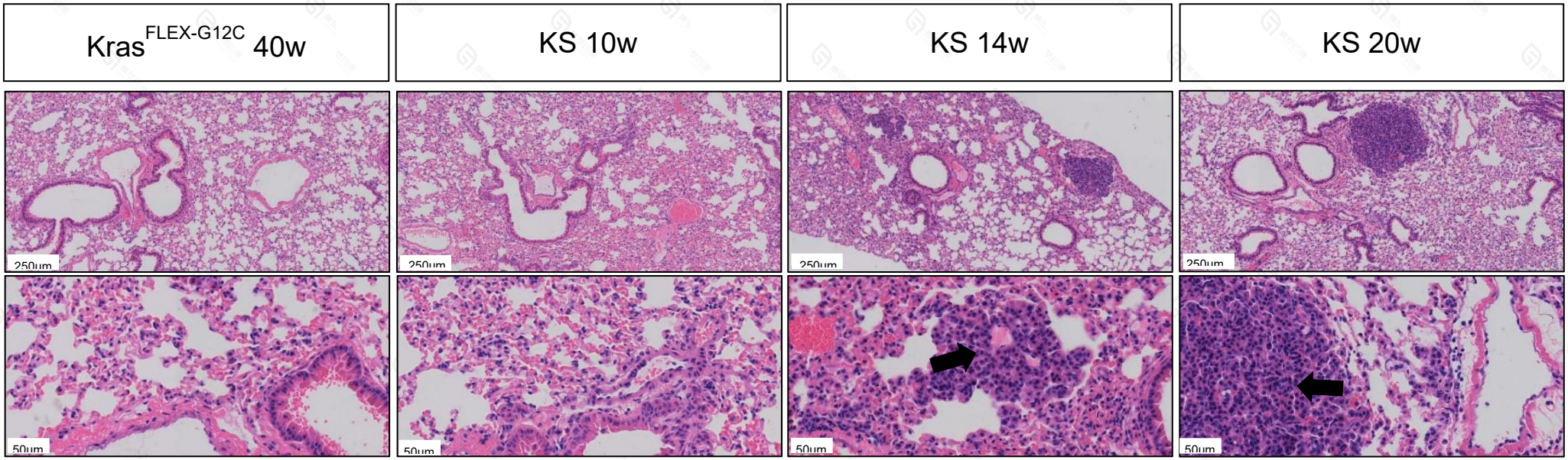

Fig 3. Detection of the lung histopathology in the KS mouse model

The lung tissues were collected from the Kras$^{FLEX-G12C}$; Sftpc-IRES-iCre mice between 10-26 weeks of age for detecting the occurrence of lung cancer. The results showed that no tumor cells were detected in the lung of 10-week-old mice. Most of the mice developed lung tumors at 14 weeks of age.

Note: Black arrows indicate the tumor cells.

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.
3. Shimshek D R, Kim J, Hübner M R, et al. "Codon‐improved Cre recombinase (iCre) expression in the mouse." genesis 2002, 32(1): 19-26.