KL

Strain Name: C57BL/6JGpt -*Kras*$^{em1Cin\ (loxP\text{-}stop\text{-}loxP\text{-}G12D)}$; *Lyz2* $^{em1Cin\ (iCre)}$/Gpt
Strain Type: Targeted
Strain Number: T007085
Background: C57BL/6JGpt

Description

KRAS (Kirsten rat sarcoma viral oncogene homolog) is a member of the RAS oncogene family and encodes a small membrane-bound GTPase that toggles between a bound state of active guanosine triphosphate (GTP) and a bound state of inactive guanosine diphosphate (GDP), which participates in the process of cell proliferation and differentiation. Mutant oncogene weakens the ability of KRAS proteins to hydrolyze GTP, which induces KRAS locked in a state of constitutive GTP-bound activity, leading to uncontrolled cell proliferation and survival. Approximately 90% of KRAS mutations occur at exon 2. In NSCL patients, KRAS G12D accounts for 23.9% of total KRAS mutations[1]. Between human and mouse KRAS, amino acid sequence similarity is 98.94%[2], therefore human and mouse KRAS proteins structures are highly similar.

Adenocarcinoma of the lung is the most common type of lung cancer. Most Lung adenocarcinomas originate from alveolar type 2 (AT2) cells or from their progenitors. lysozyme2 (LYZ2) is expressed not only in myeloid lineage but also in AT2 cells, thus LYZ2 is a surface marker of AT2[1,3,4]. It is reported that the use of a recombinant adenovirus expressing Cre recombinase (Adeno-Cre) to induce KRAS G12D expression in the lungs of mice can promote AT2 cells proliferation, which is relevant to occurrence of adenocarcinoma[5].

At present, only two small molecule inhibitors targeted to KRAS G12D have entered clinical trials. GemPharmatech establishes KL mouse model which is bred by B6-Kras-LSL-G12D mouse and Lyz2-iCre mouse. Via Cre-loxp system, KRAS G12D expressed in this mice lung. Adenocarcinoma can be detected at least the 6 weeks of age. KL mouse model can be used in research of adenocarcinoma for the drug screening.

Strategy

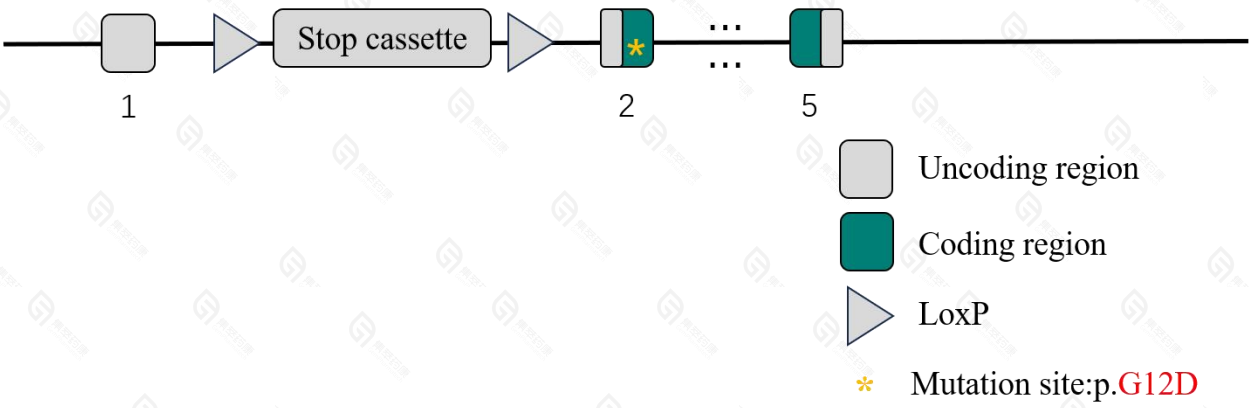

Fig.1 Schematic diagram of B6-Kras-LSL-G12D model strategy.

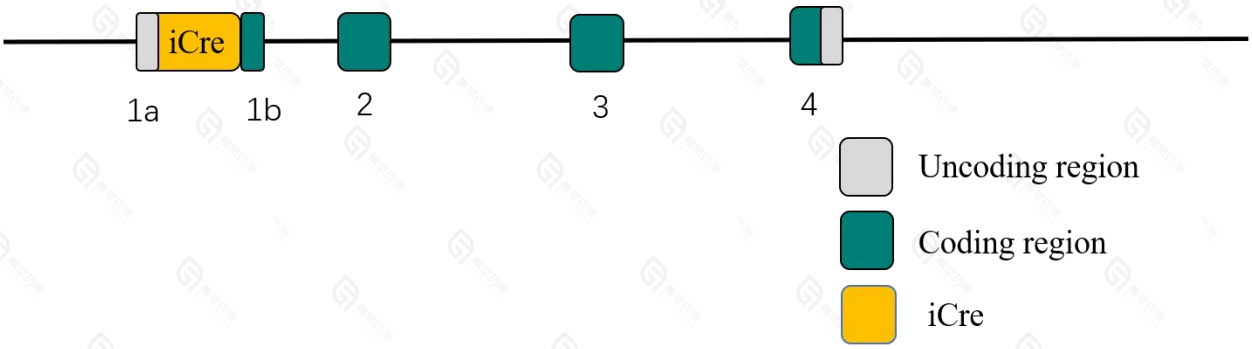

Fig.2 Schematic diagram of Lyz2-iCre model strategy.

Applications

1. Lung cancer research with KRAS G12D mutation.
2. Discovery of KRAS G12D inhibitors.
3. Discovery of KRAS G12D lung cancer immunotherapy regimen.

Data support

1. KL mice spontaneously develop lung adenocarcinoma

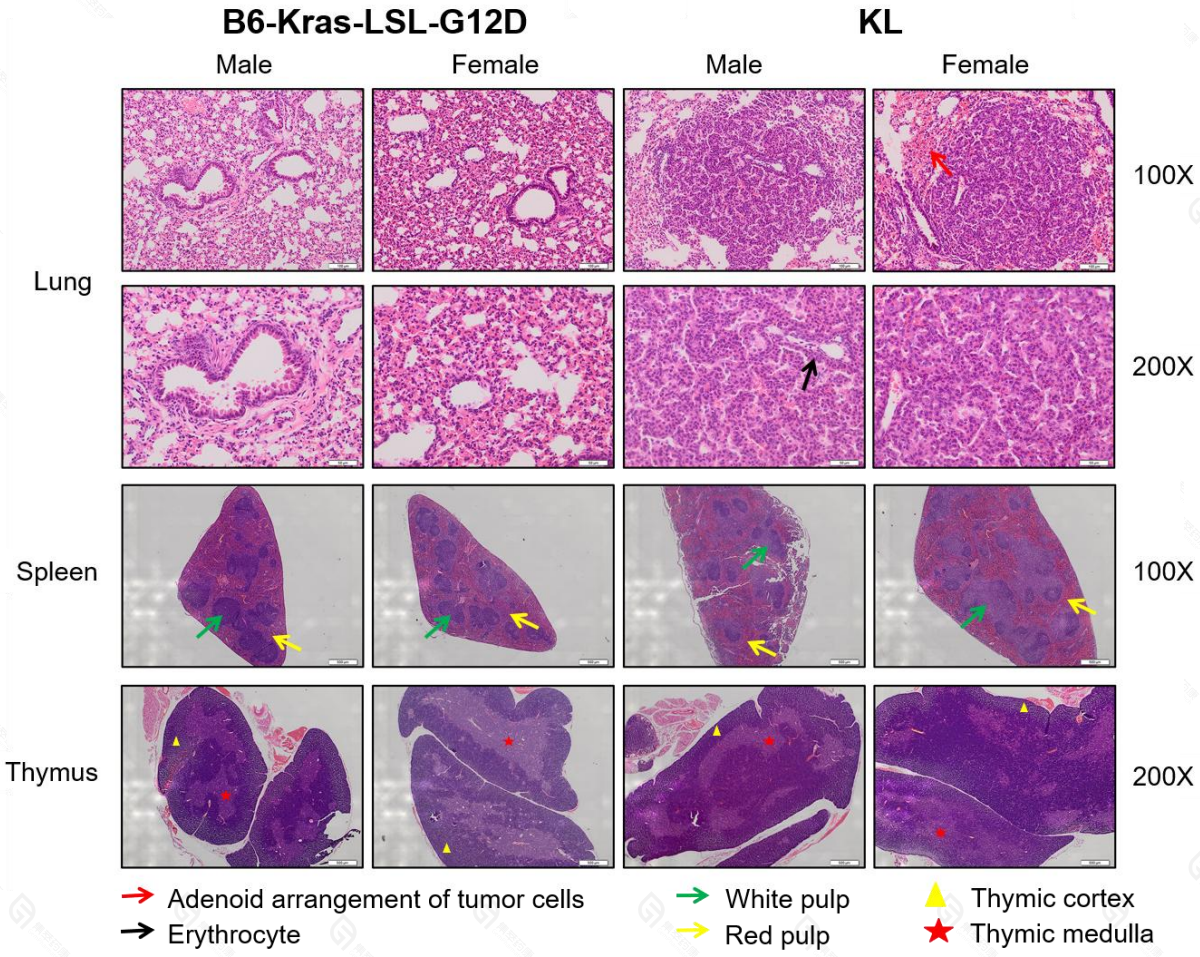

Fig 3. Pathological results of KL mice lungs, spleens, thymuses.

The lungs, spleens and thymuses were collected at KL mice 6w, 10w and 13w, then examined by HE staining for pathology analysis. It was found that the incidence of lung tumours was 100% in 3 different periods (Examples of the pathology analysis obtained from mice at 10w). The above pathological results show the tumour cells were arranged in the shape of acinar, and a large amount of inflammatory cells infiltrated the lung tissues. Spleen enlarged with increased white pulp. The cortex of thymus was thicker, and the lymphocytes were increased in the thymus. However, the lungs, spleens and thymuses of B6-Kras$^{LSL-G12D}$ were normal at the same age.

References

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2. Consortium, T.U., UniProt: the Universal Protein Knowledgebase in 2023. Nucleic Acids Research, 2022. 51(D1): p. D523-D531.
3. Menon, M.B., et al., Lyz2-Cre-Mediated Genetic Deletion of Septin7 Reveals a Role of Septins in Macrophage Cytokinesis and Kras-Driven Tumorigenesis. Front Cell Dev Biol, 2021. 9: p. 795798.
4. Spella, M., et al., Club cells form lung adenocarcinomas and maintain the alveoli of adult mice. Elife, 2019. 8.
5. Jackson, E.L., et al., Analysis of lung tumor initiation and progression using conditional expression of oncogenic K-ras. Genes Dev, 2001. 15(24): p. 3243-8.