Fah-KO

Strain Name： C57BL/6JGpt-*Fah*^{em23Cd1804}/Gpt

Strain Type： Knock-out

Strain Number： T052634

Background： C57BL/6JGpt

Description

Tyrosinemia is a disease in which the concentration of tyrosine in the plasma increases due to a defect in enzymes in the tyrosine metabolism pathway. Three different types of tyrosinemia have been discovered. Tyrosinemia type I, i.e., hepatorenal tyrosinemia (HT-1), is caused by the deficiency of fumarate acetoacetoacetic acid hydrolase (FAH), the enzyme at the very end of the tyrosine degradation pathway. FAH breaks down fumarate acetoacetate (FAA) into fumarate and acetoacetoacetic acid. Genetic mutations cause impaired or dysfunctional FAH synthesis, resulting in the accumulation of the precursor substance FAA and its derivative succinylacetone, in which further lead to hepatic, renal, and neurological symptoms [1-2]. Tyrosinemia type I is an autosomal recessive disorder with a global incidence of 1/120 000~1/100 000 [3]. Fah-KO homozygous mice have a neonatal lethal phenotype caused by liver dysfunction, and treatment with NTBC can significantly prevent neonatal lethality and recover liver function [4-5].

GemPharmatech constructed a Fah-KO mouse model on the background of C57BL/6JGpt. Fah-KO homozygous mice had no FAH protein expression in the liver and kidney. This model can simulate the pathogenesis and main symptoms of HT-1 patients, and can be used for the screening and evaluation of HT-1 therapeutic drugs.

Strategy

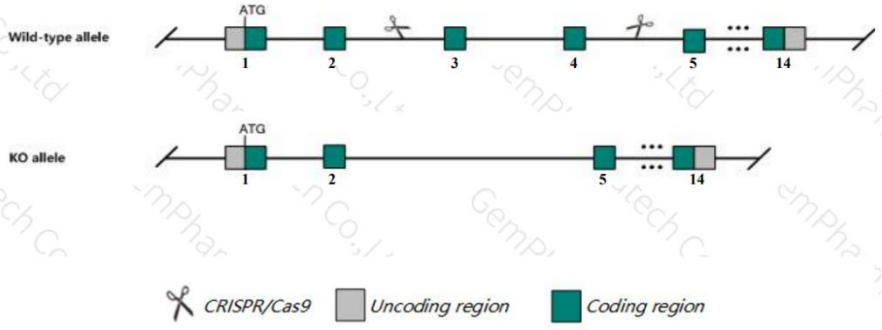


Fig.1 Schematic diagram of C57BL/6JGpt-Fah-KO model strategy.

Applications

1. Tyrosinemia type I therapeutic drug screening;
2. Evaluation of the efficacy and safety of tyrosinemia type I treatment.

Data support

1. FAH protein expression

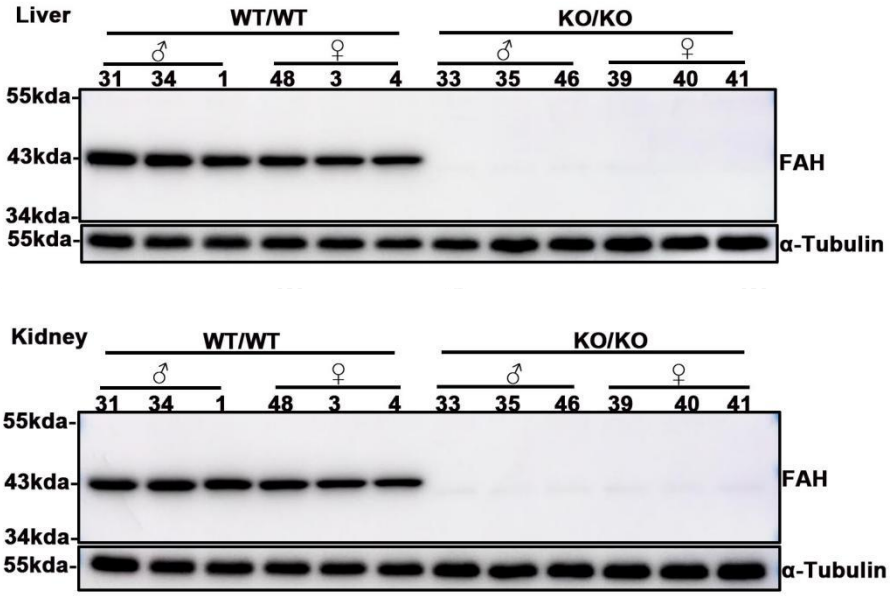
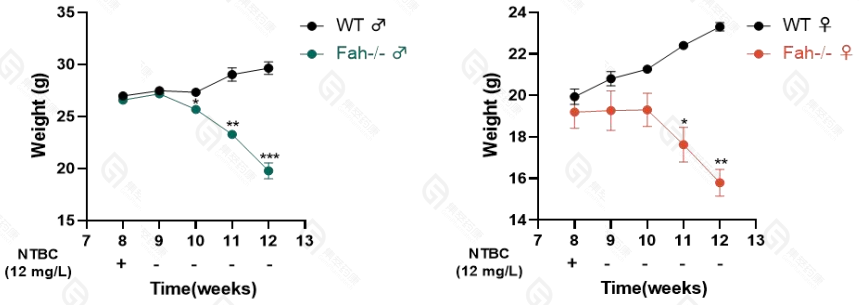


Fig.2 Expression of FAH protein in mouse liver and kidney

Western blot detection was performed on the liver and kidney of mice, and the results showed that FAH protein expression was rarely detected in the liver and kidney of Fah-KO homozygous mice, which indicated successful knocked out. WT/WT: B6J wild-type mice, KO/KO: Fah-KO homozygous mice.

2. Liver weight, kidney weight and body weight detection



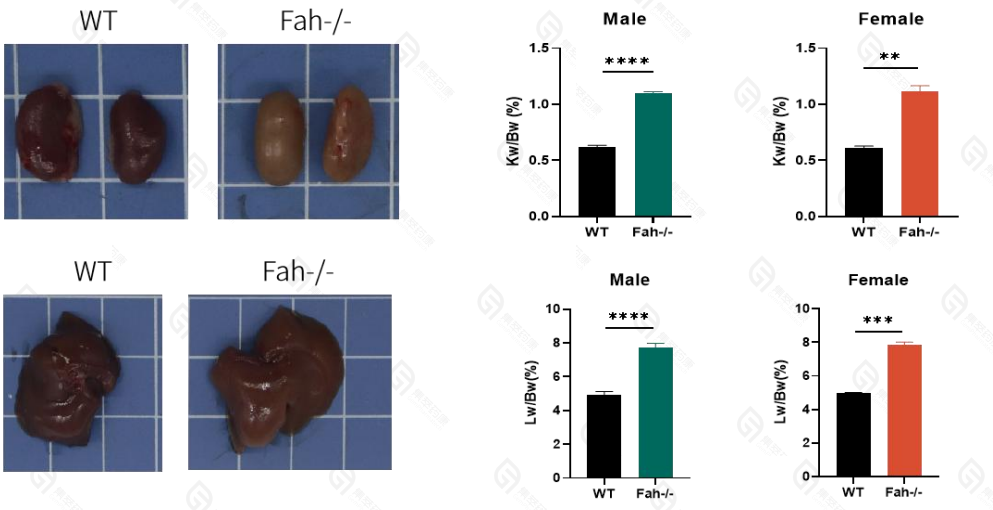
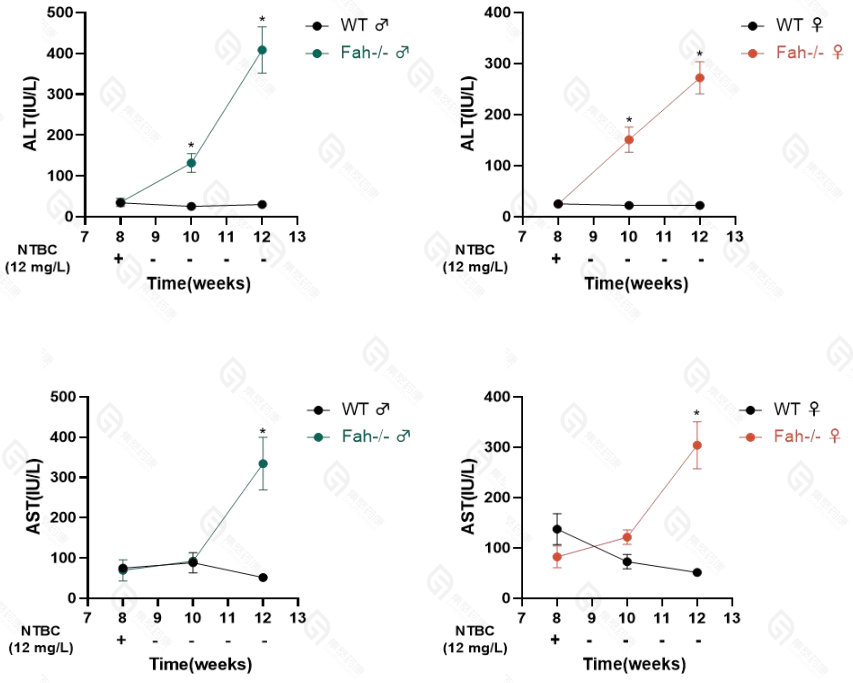


Fig.3 Detection of mouse weight, liver weight and kidney weight

After NTBC withdrawal, the weight of Fah-KO mice was gradually reduced, and the liver and kidney of the Fah-KO mice was swelled, and the liver weight/body weight and kidney weight/body weight were significantly higher than those of WT mice. WT: B6J wild-type mice, Fah-/-: Fah-KO homozygous mice. All data represent as MEAN ± SEM. Comparison between groups involved unpaired two-tailed Student's t test, * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001.

3. Liver function tests



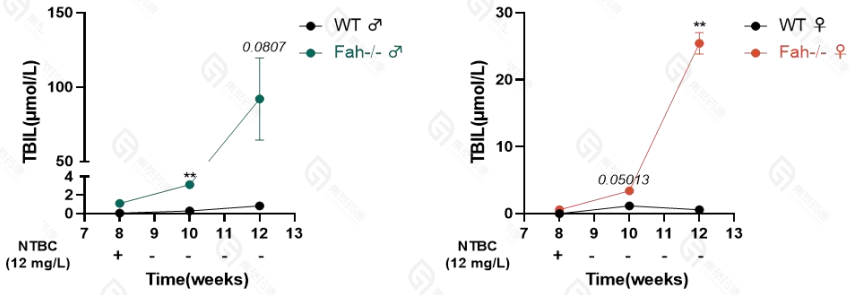


Fig.3 Detection of liver function indexes ALT, AST and TBIL

After NTBC withdrawal, the plasma levels of ALT, AST and TBIL in Fah-KO mice were significantly increased, indicating that the liver function was severely impaired. WT: B6J wild-type mice, Fah-/-: Fah-KO homozygous mice. All data represent as MEAN ± SEM. Comparison between groups involved unpaired two-tailed Student's t test, * P<0.05, ** P<0.01.

4. Liver and kidney pathology

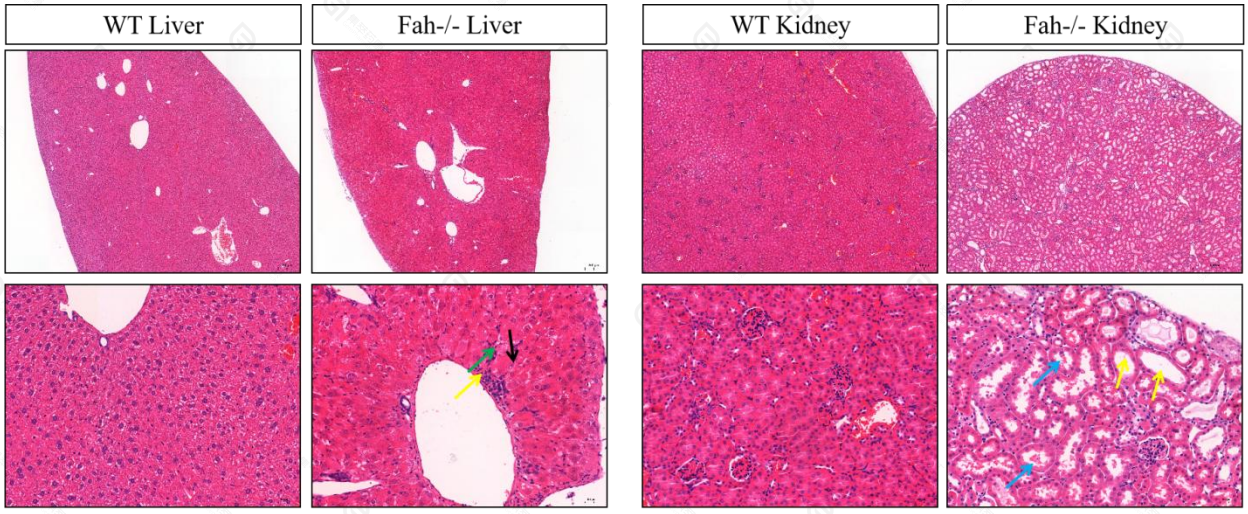


Fig.4 Pathology of HE staining in mouse liver and kidney

NTBC was discontinued for 4 weeks, and the liver and kidney of Fah-KO mice were impaired. The liver of Fah-KO mice showed hepatocyte vacuolar degeneration and slight necrosis, while the kidneys showed tubular dilation with detachment of the brush margin. WT: B6J wild-type mice, Fah-/-: Fah-KO homozygous mice.

5. Plasma tyrosine mass spectrometry detection

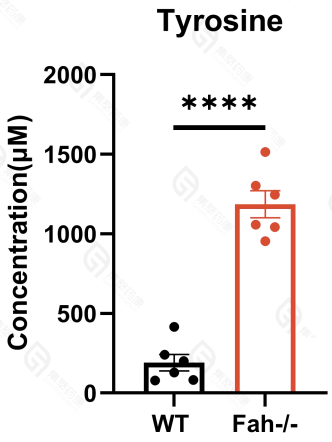


Fig.5 Plasma tyrosine concentration analysis by mass spectrometry
Four weeks after NTBC withdrawal, the plasma tyrosine concentration of 12-week-old Fah-KO mice (n=6, 3♂3♀) was significantly higher than that of WT mice (n=6, 3♂3♀). WT: B6J wild-type mice, Fah-/-: Fah-KO homozygous mice. All data represent as MEAN ± SEM. Comparison between groups involved unpaired two-tailed Student's t test, **** *P*<0.0001.

References

1. Chinsky, Jeffrey M., et al. "Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations." *Genetics in Medicine* 19.12 (2017): 1380-1395.
2. Tang, Yue, and Yuanyuan Kong. "Hereditary tyrosinemia type Ⅰ: newborn screening, diagnosis and treatment." *Zhejiang da xue xue bao. Yi xue ban= Journal of Zhejiang University. Medical Sciences* 50.4 (2021): 514-523.
3. Mitchell, Grant A., et al. "Hypertyrosinemia." *The Online Metabolic and Molecular Bases of Inherited Disease* Eds. David L. Valle, et al. McGraw Hill, 2019.
4. Grompe, Markus, et al. "Pharmacological correction of neonatal lethal hepatic dysfunction in a murine model of hereditary tyrosinaemia type I." *Nature genetics* 10.4 (1995): 453-460.
5. Tanguay, Robert M., Francesca Angileri, and Arndt Vogel. "Molecular pathogenesis of liver injury in hereditary tyrosinemia 1." *Hereditary Tyrosinemia: Pathogenesis, Screening and Management* (2017): 49-64.