H11-K18-hACE2

Stain Name：C57BL/6JGpt-*H11*$^{em1Cin(K18\text{-}hACE2)}$/Gpt

Strain Type：Knock-in

Strain ID：T037657

Background：C57BL/6JGpt

Description

SARS-CoV-2 binds to the ACE2 receptor on the surface of human cells through the spike protein (S protein), thereby entering the cell body for replication and infection, causing a cascade of immune responses and cytokine storms. Angiotensin-converting enzyme (ACE)2, also known as ACeh, is a Zn metalloprotease, which belongs to type 1 transmembrane protein. The structure includes a signal peptide, a transmembrane domain and a metalloprotease containing HEXXH zinc binding domain Active site.

The gene *ACE2* is located on the X chromosome and is mainly expressed in the gastrointestinal tract, heart, kidney, lung, testis and brain. There are key differences between human ACE2 and mouse ACE2 sequences. SARS-CoV-2, which can infect humans, may not infect mice. Therefore, wild-type mice are not suitable for virus research and vaccine development.

GemPharmatech uses gene editing technology to develop a humanized mouse model of ACE2, which simulates the clinical manifestation of human infection with the new coronavirus. ACE2 humanized mice were made on C57BL/6JGpt background mice, and the human cytokeratin 18 (Cytokeratin 18, K18) promoter was used to control the promoter to drive hACE2 overexpression at the safe island H11 site, which was used to simulate human severe COVID-19 phenotype.

Strategy

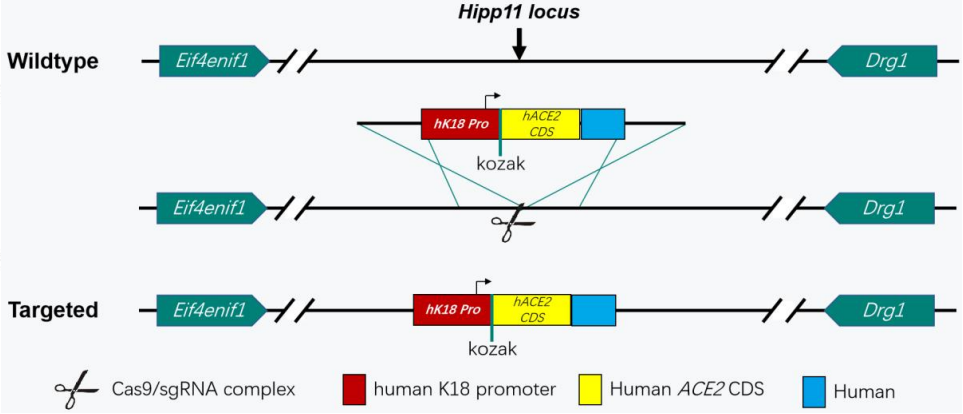


Fig1 K18-hACE2 H11 KI mice.

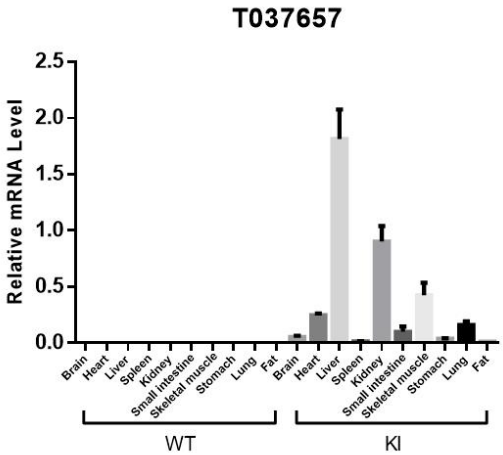
Applications

1. Study on the mechanism of SARS-CoV-2;
2. Evaluation of the efficacy and safety of SARS-CoV-2 vaccines or inhibitors;
3. Autoimmune disease research;

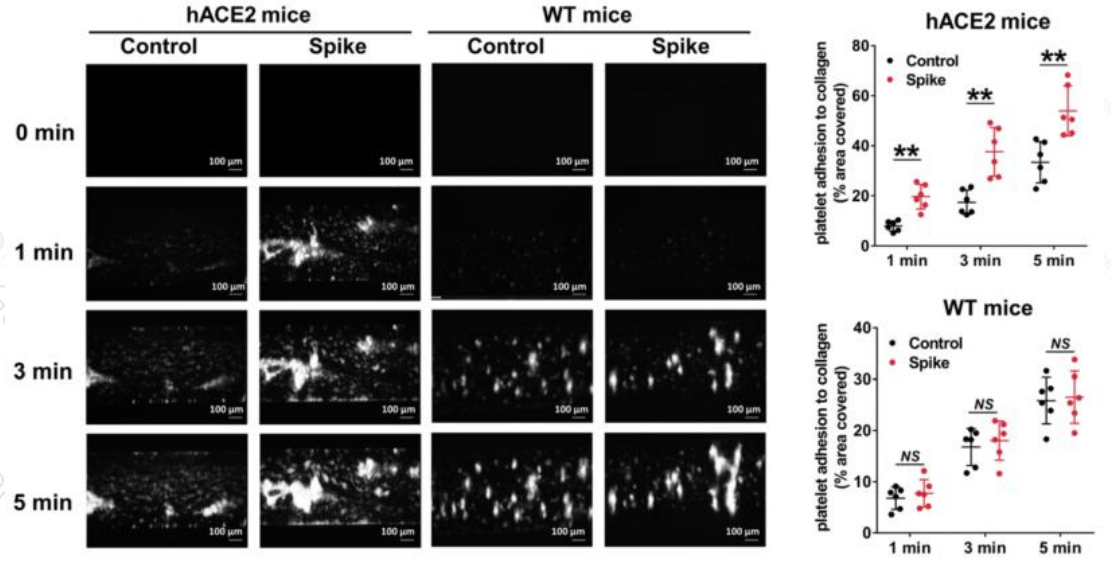
Identification

1) Mouse Age：3W-4W
2) Genotype：KI/KI，homozygote
3) Genetic Locus：*Ace2*

Data support

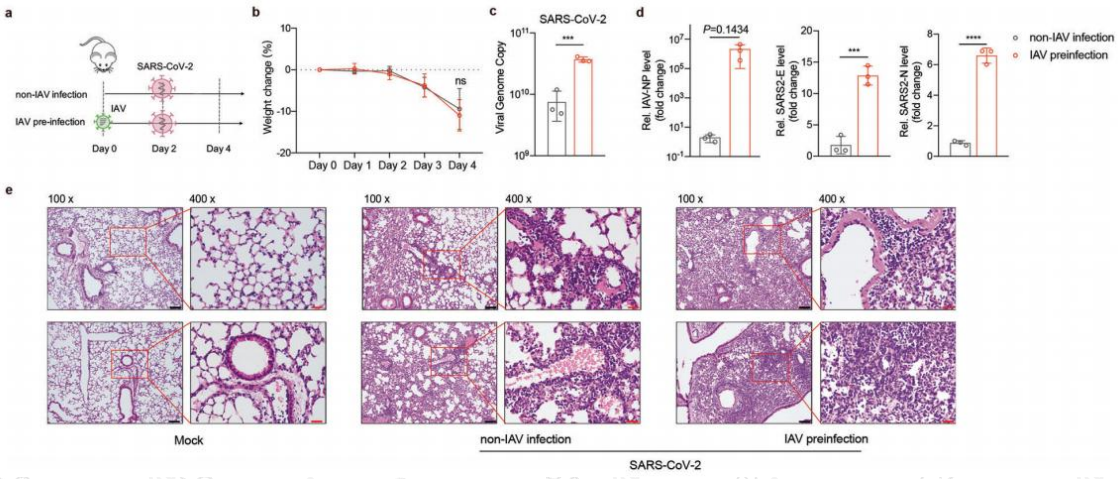


The expression of ACE2 in different tissues of H11-K18-hACE2 mice was analyzed by RT-PCR. Different degrees of expression of hACE2 were detected in liver, kidney, skeletal muscle, heart, lung and other organs, but not in control B6J mice.



S Zhang, Y Liu, X Wang, L Yang. et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol. 2020, 10. DOI:10. 21203/rs. 2. 20606/v1.

hACE2 mice quickly formed thrombus,after the spike protein was treated with whole blood



L Bai, Y Zhao, J Dong. et al. Co-infection of influenza A virus enhances SARS-CoV-2 infectivity. ACS Energy Letters. 2020, 14. doi. org/10. 1101/2020. 10. 14. 335893.

Co-infection of IAV and SARS-CoV-2 can cause more serious pathological changes in infected mice

Publications

[1] Zhang S, Liu Y, Wang X, et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. Journal of Hematology & Oncology, 2020 Sep 4;13(1):120.【IF=17.388】

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[4] Zhao S, Zhang H, Yang X, et al. Identification of potent human neutralizing antibodies against SARS-CoV-2 implications for development of therapeutics and prophylactics. Nature Communications, 2021 Aug 9;12(1):4887.【IF=14.919】

[5] Zhang L, Zhou L, Bao L, et al. SARS-CoV-2 crosses the blood–brain barrier accompanied with basement membrane disruption without tight junctions alteration. Signal Transduction and Targeted Therapy, 2021 Sep 6;6(1):337.【IF=18.187】

[6] Zhang C, Li W, Lei X, et al. Targeting lysophospholipid acid receptor 1 and ROCK kinases promotes antiviral innate immunity. Science Advances, 2021 Sep 17;7(38):eabb5933.【IF=14.136】

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[8] Pan T, Chen R, He X, et al. Infection of wild-type mice by SARS-CoV-2 B.1.351 variant indicates a possible novel cross-species transmission route.

References

[1] Zhang, S., Liu, Y., Wang, X. et al. SARS-CoV-2 binds platelet ACE2 to enhance thrombosis in COVID-19. J Hematol Oncol 13, 120 (2020). https://doi.org/10.1186/s13045-020-00954-7.

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[4] Wang et al. Chronic Activation of the Renin-Angiotensin System Induces Lung Fibrosis. Sci Rep, 2015, 5: 15561.

[5] Marshall et al. Angiotensin II and the Fibroproliferative Response to Acute Lung Injury. Am J Physiol Lung Cell Mol Physiol, 2004, 286 (1): 156-164.

[6] Kuba et al. Trilogy of ACE2: A Peptidase in the Renin-Angiotensin System, a SARS Receptor, and a Partner for Amino Acid Transporters. Pharmacol Ther, 2010, 128 (1): 119-128.

[7] Patel et al. Role of the ACE2/Angiotensin 1-7 Axis of the Renin–Angiotensin System in Heart Failure. Circ Res. 2016, 118 (8): 1313-1326.

[8] Imai et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature, 2005, 436:112-116.

[9] Kuba et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med, 2005, 11: 875-879.

[10]NetlandJ.et al. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008, 82(15):7264-7275.