Extended Methods

Isolation of porcine fetal and ear fibroblasts

Porcine fetal fibroblasts (PFFs) were isolated from 35-day-old fetuses of the Chinese Bama mini-pigs. The head, limbs, tails and viscera of the fetuses were removed, and the remaining tissues were cut into small pieces by using sterile scissors and digested in PFF culture medium containing 0.5 mg/mL collagenase IV (Life Technologies) and 2500 IU/mL DNase I (Sigma) for 4–6 h at 37 °C. The PFF culture medium contained Dulbecco's modified Eagle's medium (DMEM, HyClone), 10% fetal bovine serum (FBS, Gibco), 1% Non-Essential Amino Acids (NEAA, Gibco), 2 mM GlutaMAX (Gibco), 1 mM sodium pyruvate (Gibco), and 2% penicillin streptomycin (HyClone). Dissociated cells were centrifuged at 250 ×*g* for 5 min and plated on 10 cm culture dishes. Isolated PFFs were cultured overnight and frozen in FBS containing 10% dimethyl sulfoxide for future use.

Porcine ear fibroblasts (PEFs) were isolated from the ear tissues of the newborn piglets. Ear tissues were treated with 75% ethanol for 5 min and washed three times with containing 2% penicillin streptomycin. The ear tissues were then cut into small pieces, and digested in PFF culture medium containing 0.5 mg/mL collagenase IV and 2500 IU/mL DNase for 4–6 h at 37 °C. The isolated PEFs were cultured using procedures on PFFs.

Generation and identification of p*Rosa26*-iCas9 targeted PFF colonies

One day before electroporation, PFFs were thawed and grown in 10 cm culture dishes until 90% confluence was achieved. Approximately 1×10^6 cells were then electroporated using the Neon™ transfection system (Life Technologies) at 1350 V with 1 pulse of 30 ms duration in 100 μL of Buffer B containing 15 μg of linearized [using ApaL I restriction enzyme (Thermo

Scientific)] targeting donors and 7 μg of each TALEN. The transfected cells were divided into twenty 10 cm culture dishes and recovered for 24 h. After cell recovery, 1 mg/mL G418 (Merck) was added to the PFF culture medium. After 8–12 days of selection, G418-resistant colonies were picked and cultured in 24-well plates by using cloning cylinders. Upon 70%–80% confluency, the cell colonies were sub-cultured, and 10% of each colony was lysed individually in 10 μL of NP-40 lysis buffer (0.45% NP-40 plus 0.6% Proteinase K) for 60 min at 56 °C and then for 10 min at 95 °C. The lysate was used as a template for PCR screening, which was performed using Long PCR Enzyme Mix (Thermo Scientific), in accordance with the manufacturer's instructions. PCR analysis was used to confirm HDR with the 5′ junction primers (F1: 5′-TGCGTGAGTCTCTGAGCGCAG-3′, R1: 5′-GGCATCAGAGCAGCCGATTGT-3′), the 3′ junction primers (F2: 5′-GATGCTGTGCCGGTCGGTGTT-3′, R2: 5′-GGTCAAACAGTGGCTCACATCT-3′). The PCR conditions were 95 °C for 5 min; 98 °C for 10 s, 68 °C for 30 s (−0.6 °C/cycle), 68 °C for 2 min (5-arm)/6 min (3-arm), for 35 cycles; and 72 °C for 10 min; held at 12 °C. To determine the occurrence of monoallelic or biallelic targeting, competitive PCR was performed using the primers F2 + F + R (F2: 5′-GATGCTGTGCCGGTCGGTGTT-3′, F: 5′-CTCGTCATCGCCTCCATGTCAG-3′, R: 5′-GTTGGGCCTATGCTCAAGATGG-3′) (monoallelic targeting: 892 and 590 bp; biallelic targeting: 892 bp; wild-type: 590 bp). The PCR conditions were 95 °C for 5 min; 98 °C for 10 s, 68 °C for 30 s (−0.6 °C/cycle), 68 °C for 1 min, for 35 cycles; 72 °C for 5 min; held at 12 °C. The positive cell colonies were expanded and cryopreserved in liquid nitrogen for further SCNT.

Design and construction of sgRNA vectors.

U6-sgRNA cloning vector was purchased from Addgene (Addgene: 41819). In this vector, two BbsI restriction sites were located at the downstream region of U6 promoter. *GGTA1*-sgRNA, *APC*-sgRNA, *BRCA1*-sgRNA, *BRCA2*-sgRNA, *EML4*-sgRNA, *ALK*-sgRNA, *TP53*-sgRNA, *PTEN*-sgRNA and *KRAS*-sgRNA were designed using the G-N19-NGG rule. A pair of complementary oligonucleotides of sgRNA were synthesized and annealed at 98 °C for 5 min and then ramped down to 4 °C to generate the double-strand DNA, which was cloned into the BbsI-digested U6-sgRNA cloning vector. These constructed plasmids were further confirmed by Sanger sequence analysis. The primers used in this study are listed in Supplemental Table 3.

Construction and preparation of lentiviral vector PPK and AB12

Briefly, all PCR products of sgRNA expression cassette contained BsmB I restriction enzyme sites. Mix 150 ng of FUGW-Cre-T2A-EGFP + 150 ng of PCR products of *TP53*-sgRNA, *PTEN*-sgRNA, *KRAS*-sgRNA (or FUGW-Cre-T2A-EGFP + PCR products of *APC*-sgRNA, *BRCA1*-sgRNA, *BRCA1*-sgRNA) + 1μL BsmB I (NEB) + 1μL T4 DNA ligase (NEB) + 2μL T4 DNA ligase buffer in PCR tubes and the total reaction volume is 20μl. Run the cycle: 5 × (37˚C/5min + 16˚C/10min) + 55˚C/5min + 80˚C/5min. To avoid unwanted recombination, Stbl3 chemically competent *E. coli* were used for lentiviral plasmid PPK and AB12 construction and preparation.

Cell infection and FACS.

For infection of p*Rosa26*-iCas9 fibroblasts with purified lentiviruses, we seeded 5×10^4 fibroblasts into six-well dishes. After 24 h, p*Rosa26*-iCas9 fibroblasts were incubated for 6 h by using a diluted viral stock. Polybrene (8 μg/mL, Sigma) was added to increase the infection

efficiency. At 7 days post-infection, fibroblasts were analyzed by fluorescence microscopy and flow cytometry. For FACS, cells were trypsinized and washed twice with PBS. Afterward, EGFP and tdTomato expression were analyzed by flow cytometry.

Genomic DNA extraction and indel analysis

Genomic DNA from both cells and tissues was extracted using TIANGEN genomic DNA extraction kit following the manufacturer's recommendation. p*Rosa*26-iCas9 fibroblasts and tissues infected by lentivirus were used as PCR templates for both captured sequencing and T7EN1 cleavage assay by using high-fidelity polymerases (KOD-Plus-Neo, TOYOBO). Selected PCR products were ligated into pMD18-T vector (Takara) and further sequenced to determine the exact mutant sequences.

Western blot analysis

Cells were lysed in RIPA buffer supplemented with protease and phosphatase inhibitors (Roche) on ice for 15 min. The protein lysates were mixed with SDS loading buffer (62.6 mM Tris-HCl, 10% glycerol, 0.01% bromophenol blue, 2% SDS, pH 6.8) after determining the protein concentration following the Lowry method (Bio-Rad). The samples were boiled for 15 min, loaded onto SDS-PAGE gels for separation, and then transferred to nitrocellulose membrane. The membranes were blocked with 5% skim milk in TBST for 2 h. PVDF was then incubated with the primary antibody for 2 h (rabbit anti-CRISPR-Cas9 antibody, Hangzhou HuaAn Biotechnology Company; mouse anti-a-Gal Epitope antibody, M86, Enzo). After rinsing three times with TBST, the membrane was incubated for 1 h at room temperature with HRP-conjugated secondary antibodies and then rewashed with TBST three times. The signal was visualized using ECL plus (Amersham) in accordance with the manufacturer's instructions.

T7EN1 cleavage assay

Lentivirus infected cells were harvested and genomic DNA was extracted using TIANGEN genomic DNA extraction kit. The T7EN1 cleavage assay was performed as previously reported. Briefly, PCR products around the target sites were amplified using the primer pairs listed in Supplemental Table 3 and purified using TIANGEN PCR cleanup kit following the manufacturer′s recommendations. Purified PCR products were denatured and annealed to form heteroduplex DNA in NEBuffer2 (New England Biolabs) by using a thermocycler with the following protocol: 95 °C, 5 min; 95 °C to 75 °C at −2 °C/s; 75 °C to 16 °C at −0.1 °C/s; and then held at 4 °C. Hybridized PCR products were treated with 5 U of T7 Endonuclease I at 37 °C for 15 min. Products were separated using 2% agarose gel and then detected by ethidium bromide staining. The was calculated using the following formula: Cleavage efficiency (%) = 100 × [1-(1-fraction cleaved)$^{1/2}$]

RT-PCR

RT-PCR was conducted to investigate the expression profiles of porcine *EML4* and *ALK*. Total RNAs were extracted from *EML4*-sgRNA or/and *ALK*-sgRNA lentiviruses infected p*Rosa26*-fibroblasts by using TRIzol Reagent (LifeTechnologies). Genomic DNA was digested with DNaseI. cDNAs were then prepared using PrimeScript™ II Reverse Transcriptase kit (Takara). The primers used to amplify the porcine *EML4-ALK* fusion transcripts were *EML4*-F: 5′-TGGGGAATGGAGATGTGCTT-3′ and *ALK*-R: 5′-TGAGGGTGATGTTTTTCCGAG-5′. The porcine glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) was used as the control gene (GAPDH-F: 5′-GATGGCCCCTCTGGGAAACTGTG-3′; GAPDH-R: 5′-GGACGCCTGCTTCACCACCTTCT-3′). The RT-PCR products were predicted to be 279 bp

(*EML4-ALK* fusion transcripts) and 234 bp (*GAPDH*) and then sequenced by BGI.

Targeting Vector Sequences

Elements:

p*Rosa26* left arm

SA

*lox*P

Neomycin

SV40 polyA

*lox*P2272

inverted polyA

inverted tdTomato

inverted T2A

inverted SpCas9

p*Rosa26* right arm

PGK promoter

DTA

PGK-polyA

GAGGCTGTGCTCTGGGGCTCCGGCTCCTCAGAGAGCCTCGGCTAGGTAGGGGAGC

GGGACTCTGGTTTGGGGGAGGGCCGGCGGTTTGGCGGGGGATGGGTGCTTGAGG

TGGTCTGACCGGTAGCGGGGGTCGCCTTCCCTAGCGGGAAGTCGGGAGCATATCG

TTTGTTACGCTGGAAGGGGAAGAGGTGGTGAGAGGCAGGCGGGAGTGCGGCCCG

CCCTGCGGCAACCGGAGGGGGAGGGAGAAGGGAGCGGAAAAGCCTGGAATACG

GACGGAGCCATTGCTCCCGCAGAGGGAGGAGCGCTTCCTGCTCTTCTCTTGTCAC

TGATTGGCCGCTTCTCCTCCCGCCGTGTGTGAAAACACAAATGGCGTGTTTTGGTT

GGAGTAAAGCTCCTGTCAGTTACAGCCTCGGGAGTGCGCAGCCTCCCAGGAACTC

TCGCATTGCCCCCTGGGTGGGTAGGTAGGTGGGGTGGAGAGAGCTGCACAAGAG

GGCGCTGTCGGCCTCCTGCGGGGGGAGGGGAGGGTCAGTGAAAGTGGCTCCCGC

GCGGGCGTCCTGCCACCCTCCCCTCCGGGGGAGTCGGTTTACCCGCCGCCTGCTC

GGCTTTGGTATCTGATTGGCTGCTGAAGTCCTGGGAACGGCCCCTTGTTATTGGCT

TGGGTCCCAAATGAGCGAAACCACTACGCGAGTCGGCAGGGAGGCGGTCTTTGGT

ACGGCCCTCCCCGAGGCCAGCGCCGCAGTGTCTGGCCCCTCGCCCCTGCGCAACG

TGGCAGGAAGCGCGCGGCAGGAGGCGGGGGCGGGCTGCCGGGCCGAGGCTTCTGG

GTGGTGGTGACTGCGGCTCCGCCCTGGGCGTCCGCCGCCTGAAGGACGAGACTAG

CTCTACCTGCTCTCGGACCCGTGGGGGTGGGGGGTGGAGGAAGTGAGTGGGGGG

TCGGTCCTGCTGGCTTGTGGGTGGGAGGCGCATGTTCTCCAAAAACCCGCGCGAG

CTGCAATCCTGAGGGAGCTGCAGTGGAGGAGGCGGAGAGAAGGCGCACCCTTCT

CCGCAGGGGGAGGGGAGTGCCGCAATACCTTTATGGGAGTTCTCTGCTGCCTCCTT

TTCCTAAGGACCGCCCTGGGCCTAGAAAAATCCCTCCCTCCCCCGCGATCTCGTCA

TCGCCTCCATGTCAGTTTGCTCCTTCTCGATTATGGGCGGGATTCTTTTGCCCTGGC

TTAACCTGATTCTTGGGCGTTGTCCTGCAGGGTGACCTGCACGTCTAGGGCGCAGT

AGTCCAGGGTTTCCTTGATGATGTCATACTTATCCTGTCCCTTTTTTTTCCACAGCTC

GCGGTTGAGGACAAACTCTTCGCGGTCTTTCCAGTAAGAATTCCTCGATCGAGGG

ACCTAATAACTTCGTATAGCATACATTATACGAAGTTATATTAAGGGTTCCGCAAGCT

TGCAGCCAATATGGGATCGGCCATTGAACAAGATGGATTGCACGCAGGTTCTCCGG

CCGCTTGGGTGGAGAGGCTATTCGGCTATGACTGGGCACAACAGACAATCGGCTG

CTCTGATGCCGCCGTGTTCCGGCTGTCAGCGCAGGGGCGCCCGGTTCTTTTTGTCA

AGACCGACCTGTCCGGTGCCCTGAATGAACTGCAGGACGAGGCAGCGCGGCTATC

GTGGCTGGCCACGACGGGCGTTCCTTGCGCAGCTGTGCTCGACGTTGTCACTGAA

GCGGGAAGGGACTGGCTGCTATTGGGCGAAGTGCCGGGGCAGGATCTCCTGTCAT

CTCACCTTGCTCCTGCCGAGAAAGTATCCATCATGGCTGATGCAATGCGGCGGCTG

CATACGCTTGATCCGGCTACCTGCCCATTCGACCACCAAGCGAAACATCGCATCGA

GCGAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCAGGATGATCTGGACGAA

GAGCATCAGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAAGGCGCGCATGC

CCGACGGCGAGGATCTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATCATG

GTGGAAAATGGCCGCTTTTCTGGATTCATCGACTGTGGCCGGCTGGGTGTGGCGG

ACCGCTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGCGGC

GAATGGGCTGACCGCTTCCTCGTGCTTTACGGTATCGCCGCTCCCGATTCGCAGCG

CATCGCCTTCTATCGCCTTCTTGACGAGTTCTTCTGAGGGGATCGGCAATAAAAAG

ACAGAATAAAACGCACGGGTGTTGGGTCGTTTGTTCGGATCTAGACTAGATCATAA

TCAGCCATACCACATTTGTAGAGGTTTTACTTGCTTTAAAAAACCTCCCACACCTCC

CCCTGAACCTGAAACATAAAATGAATGCAATTGTTGTTGTTAACTTGTTTATTGCAG

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