Supplementary methods

1. Myocardial infarction model

C57BL/6 male mice (8–10 weeks, Charles River Laboratories) were used to build MI model. Before the operation, the weight of the mice was assessed with an electronic balance, then the hair on the chest of the mouse was removed, and the mouse was anesthetized with isoflurane at a concentration of 1.5%-2.0% according to the weight of mice by applying an isoflurane ventilation system (RWD Life Science, Shen Zhen). After the mice collapsed, breathing was steady and slow, and muscle strength decreased, a small incision was made by scissors on the left chest. After the fourth intercostal space was exposed, and the pleura and pericardium were opened by mosquito forceps, the left anterior descending branch (LAD) could be visualized, and ligated with a 6-0 silk thread at the site of 2mm below the left atrial appendage. The pale anterior wall of the left ventricle and the elevated ST segment in electrocardiogram were showed, which meant MI model was successfully built. After ligation, we put the heart back into the chest cavity immediately, manually evacuated the air in the chest cavity, and sutured the skin with a 4-0 silk thread. The sham operation group received the same surgical operation, except for ligation of LAD. At the specified time-points, these mice were anaesthetised by intraperitoneal injection of pentobarbitone sodium solution (100mg/kg). Upon deep anaesthesia (loss of the pedal pain, slowing of breathing and heart rate), these mice were euthanized by excising the heart for further analysis.

2. *Culture of primary neonatal rat cardiomyocytes (NRCMs) and cardiac fibroblasts (NRCFs) for analysis*

In brief, the hearts were taken quickly, and washed by PBS twice, then minced into small pieces, and incubated with 0.125% trypsin at 37ºC for 8 min of digestion. The cells were collected by centrifugation. The digestion procedure was repeated for 5-7 times. All the cells were seeded in a10-cm dishe. After 1.5 hour of attachment in 37 ℃, the attached fibroblasts were cultured in DMEM/F12 medium (10% FBS, 1% antibiotics). Non-attached cardiomyocytes were gathered by centrifugation and re-suspended in the same culture medium to seed in 6-well plates. After 48 h, the culture medium was changed to FBS-free DMEM for 12h starvation for the following experiment.

Fibroblasts of second generation were used in all subsequent experiments. The fibroblasts were cultured in DMEM medium (10% FBS, 1% antibiotics) to get 80-90% confluence, then moved to serum-free DMEM for 12h starvation before treatment with different concentrations of recombinant human Wnt2 protein (Cat#: H00007472-P01, Abnova) or human Wnt4 protein (Cat#: 6076-WN, R&D Systems). For inhibition of NF-κB or β-catenin study, cardiac fibroblasts were treated with JSH-23(10μM, Cat#: HY-13982, MedChemExpress, USA) or ICG-001(10μM, Cat#: S2662, Selleck, USA) and DMSO, respectively, for 1 h before human recombinant Wnt2 or Wnt4 protein treatment. For protein synthesis inhibitor study, cardiac fibroblasts were treated with Cycloheximide(CHX) (50μM, Cat#: S7418, Selleck, USA) or DMSO for 0.5 h before incubation of human recombinant Wnt2 or Wnt4 protein. At indicated time-points, fibroblasts were collected for subsequent analysis. For Wnt-C59 (C59) inhibitor study, cardiac fibroblasts were treated with C59 (20μM, Cat#: HY-15659, MedChemExpress,

USA) or DMSO for 1h and then they were moved to hypoxic incubator for 6h. The control group was placed at a normoxia incubator.

3. Isolation of cardiomyocytes and fibroblasts from adult mouse

Briefly, male C57BL/6 mice of 8 weeks old were euthanized, and the heart was exposed. After 7ml of EDTA was injected into the right ventricle,quickly. 10 mL of EDTA, 3 mL of perfusion buffer, followed by 50 mL of collagenase buffer were injected from the apex of the left ventricle to digest the heart. Heart tissues were cut into $1mm^3$ pieces after enough digestion. Perfusion buffer containing 5% FBS was used to stop digestion and cell suspension was passed through a disposable sterile 100um strainer. After 20 minutes, non-cardiomyocytes in supernatant were removed into other tubes for centrifugation and collection. Cardiomyocytes at the bottle of centrifuge tube were collected for analysis.

4. Wheat germ agglutinin (WGA) staining

Lyophilized powder of WGA (Cat#: L4895. Sigma. USA)was diluted with PBS (5.0ug/ml). We washed the frozen heart sections 3 times with PBS, and then incubated them with sufficient amount of WGA solution for 10 minutes at room temperature. After washing, we captured digital images using a fluorescence microscope (Nikon, A1R, Japan).

5. Luciferase reporter assay

COS-7 cell line (RRID: CVCL_0224; Cell Bank, Type Culture Collecting, Chinese Academy Science, SCSP-508) was validated and used to perform luciferase reporter assay. Before assay, the cell line was tested for mycoplasma in 2021 and the result was

negative. The cells were cultured in 24-well plates to reach a concentration of 10^5. The topflash plasmid (Cat#: HG-VXM0654, Honorgene, Changsha) carrying firefly luciferase gene reporter or fopflash plasmid (Cat#: HG-VXM0655, honorgene, Changsha) combined with pRL-TK plasmid (Cat#: HG-VQP0126, promega, U.S.A) were transfected into COS-7 cells with Lipofectamine™ 3000 Reagent (Cat#: L3000015, Ambion Inc, Texas, U.S.A) according to the manufacturer's instructions. After 24 hours, the culture medium was changed with FBS-free DMEM. After 48 hours, we added Wnt2(20ng/ml) or Wnt4(50ng/ml) to the transfected cells and harvested them after 8 hours of stimulation. Luciferase activity was recorded with Dual-Luciferase Reporter Assay kit (Cat#:1910, Promega, U.S.A) on biotek luminometer according to the manufacturer's protocol.

6. SiRNA transfection

Briefly, the siRNA (30pmol in 150 μl opti-MEM) and transfection reagent (Cat#:13778150, Lipofectamine™ RNAiMAX, Ambion Inc, Texas, U.S.A, 9ul in 150 μl opti-MEM) were gently mixed, and incubated at room temperature for 5 minutes, then were added into cultured cells. 24h later, we replaced the medium with fresh DMEM containing 10% FBS for subsequent experiments on transfected cells.