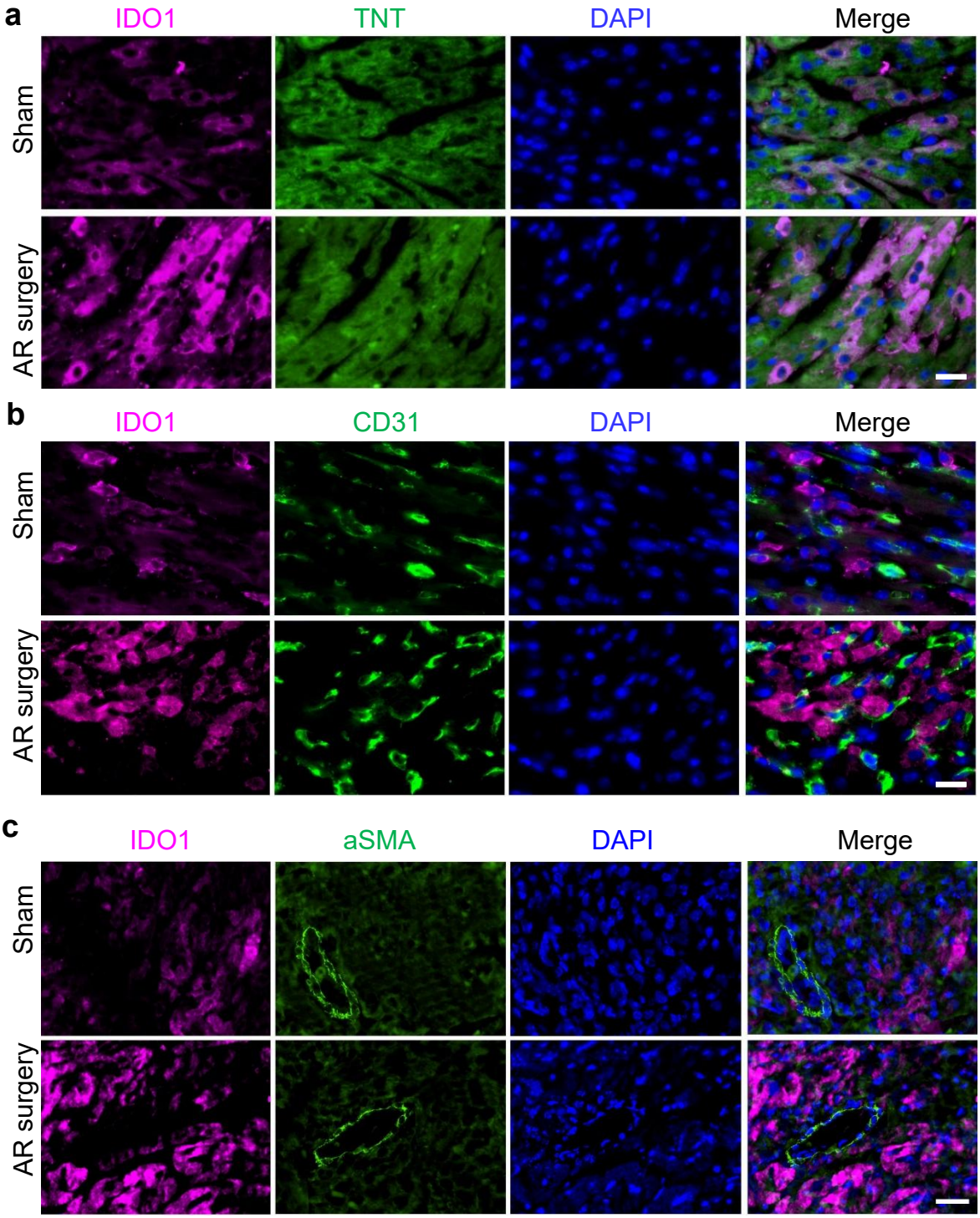
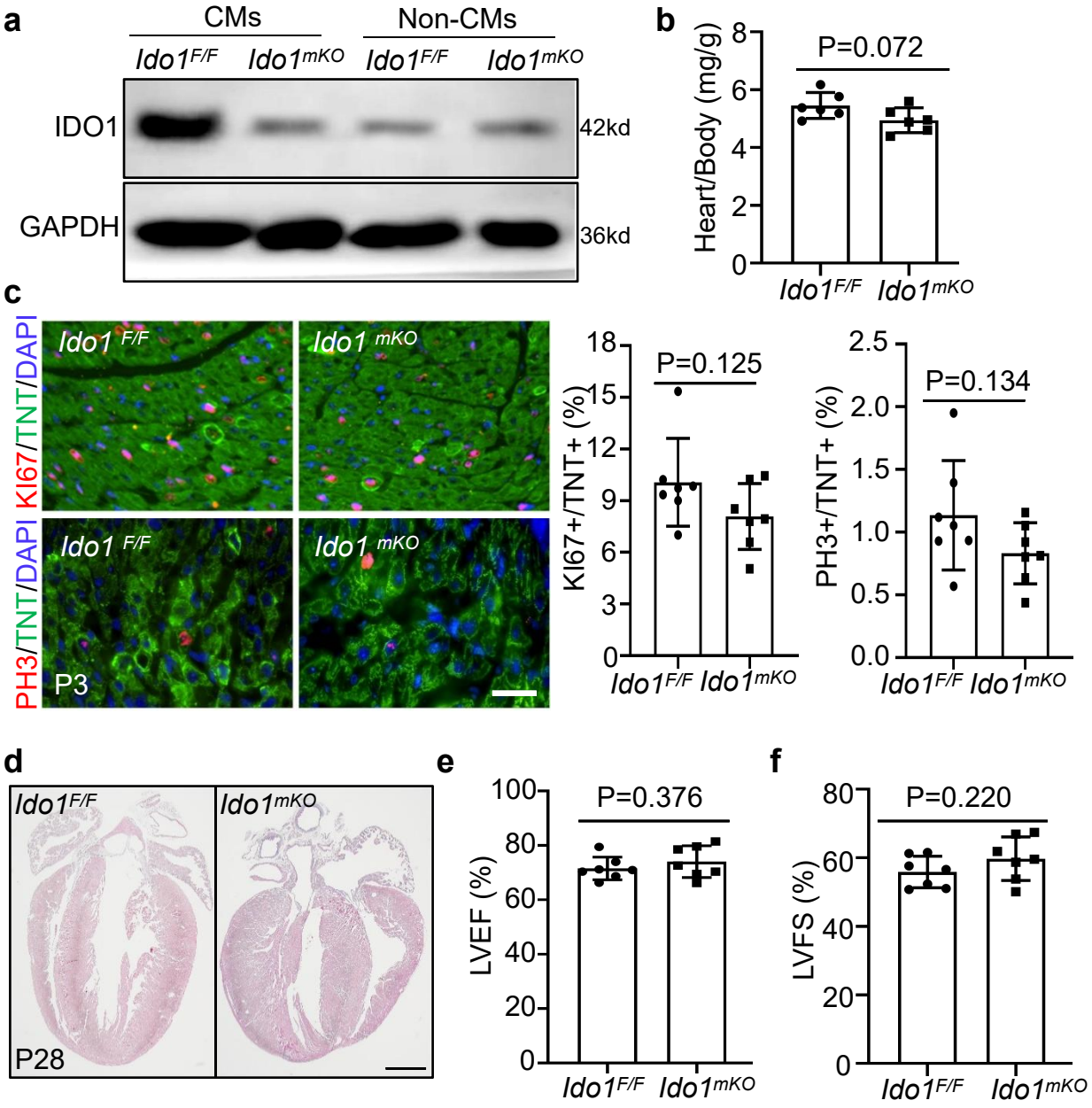
Supplementary Information

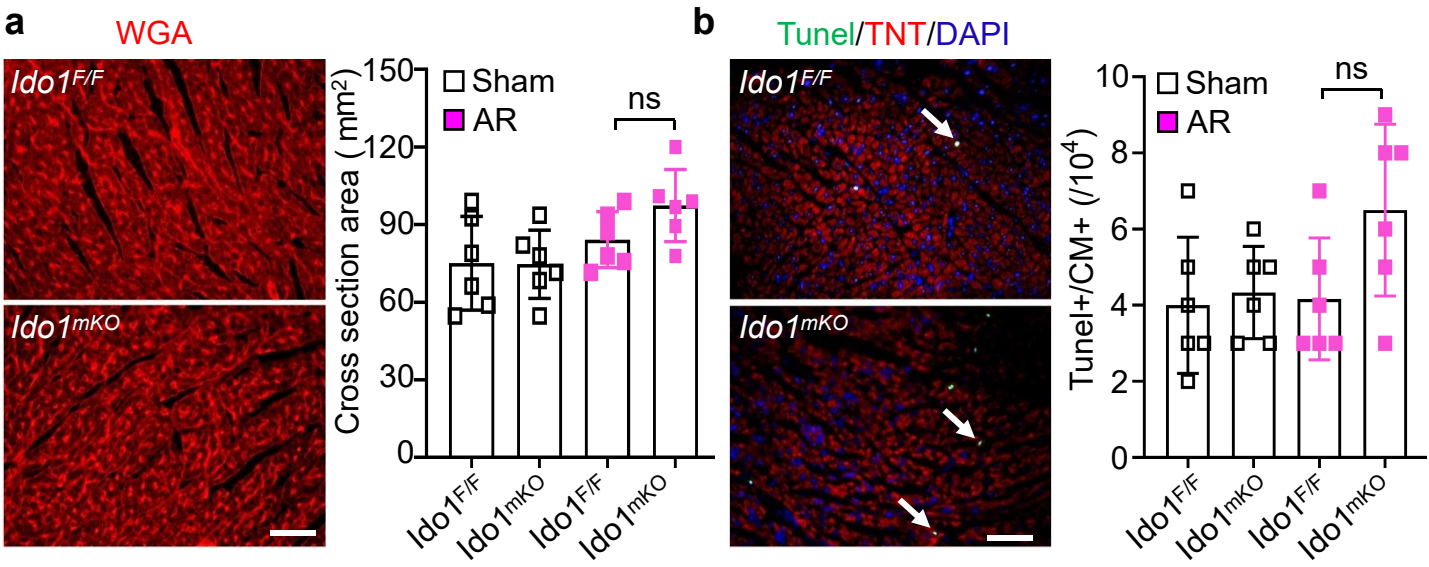
Supplementary Figs and Figure Legends



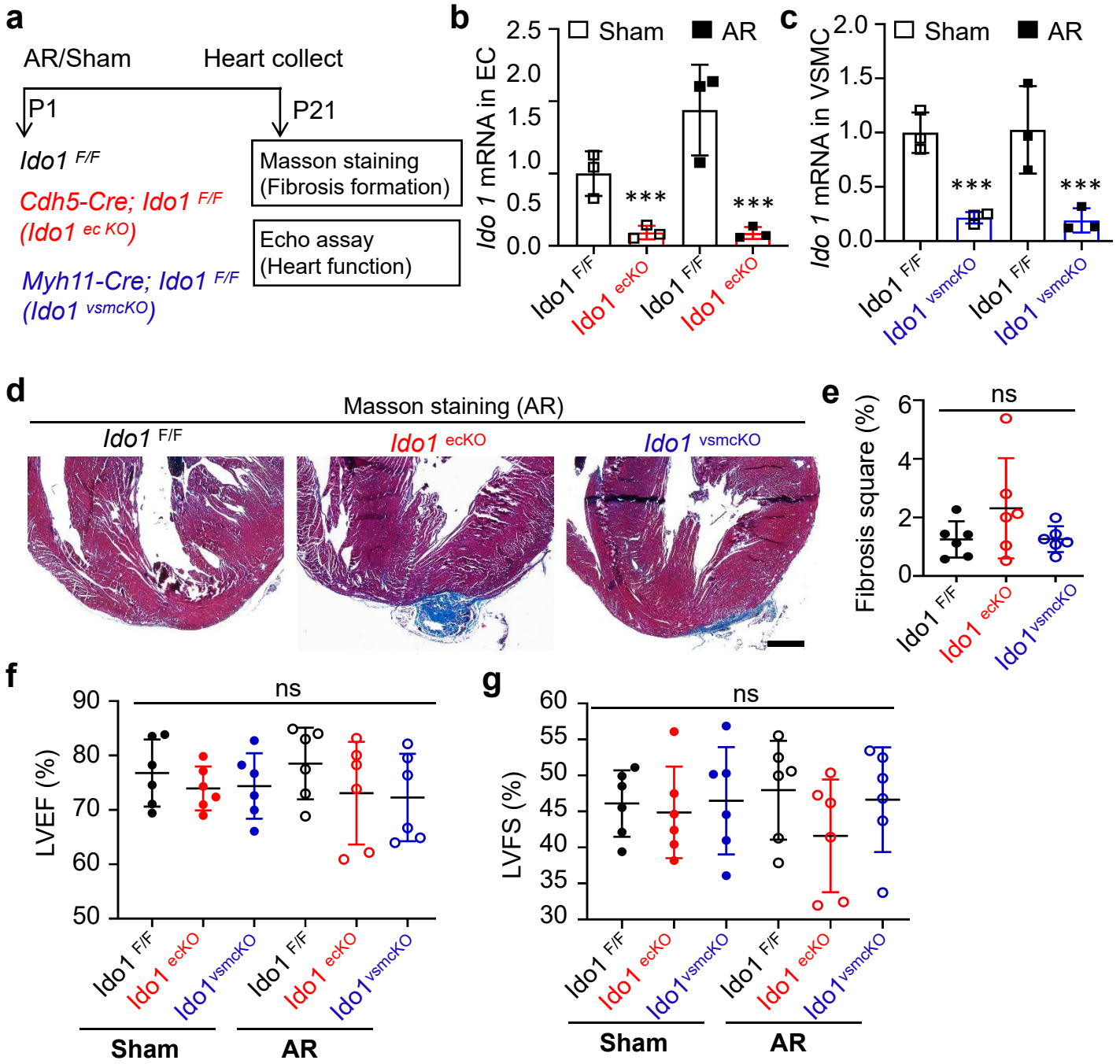
Supplementary Fig. 1. Elevated Ido1 localizes in regenerated cardiomyocytes (CMs), but not in endothelial cells (ECs) or vascular smooth muscle cells (VSMCs) after heart apical resection (AR) or Sham surgery at postnatal 1 day (P1). a-c, Representative co-immunostaining of IDO1 with Troponin T (TNT, **a**), CD31 (**b**) and αSM-actin (αSMA, **c**) in the apical heart at P7. All immunostaining were performed on four sections per sample and four images were taken from different fields per section. Four samples of each group were experimented. Bar= 20 μm.



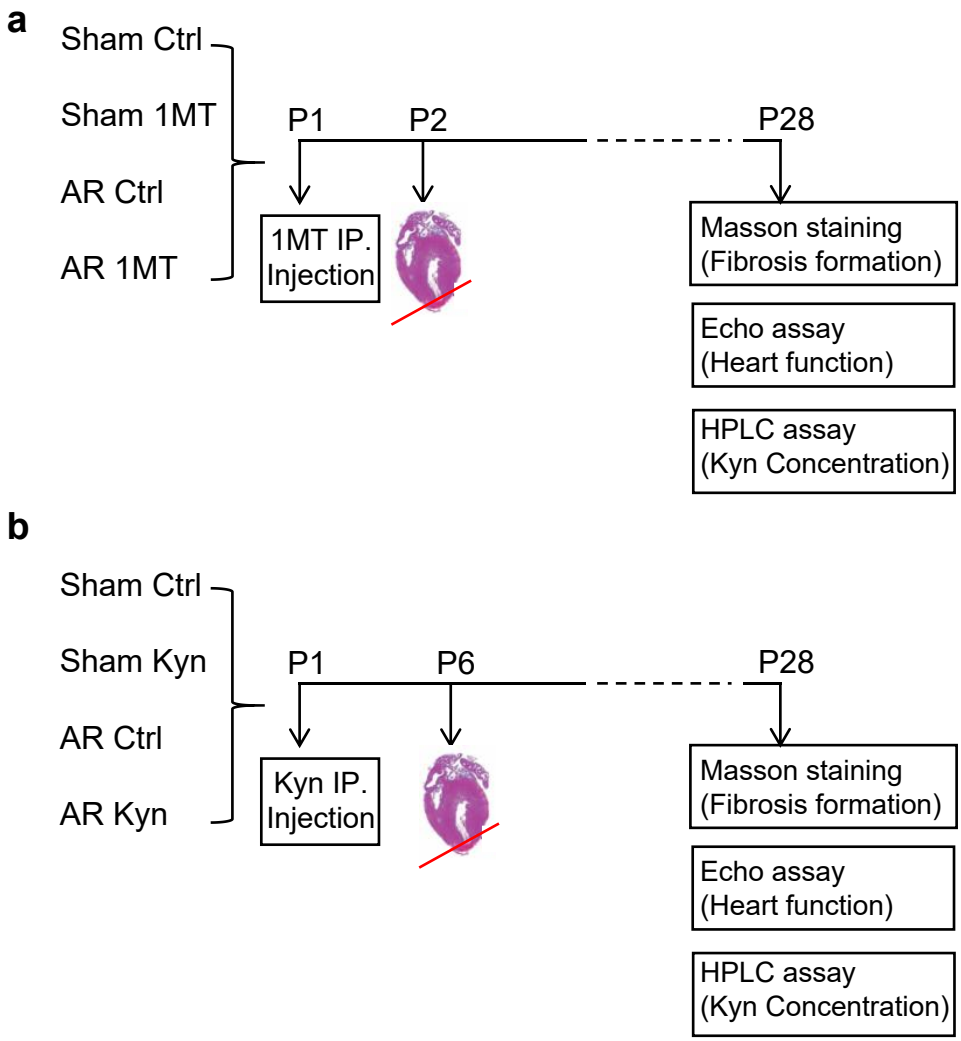
Supplementary Fig. 2. Cardiac-specific *Ido1* knockout mice develop normally. **a,** Western blot analysis of IDO1 expression in cardiomyocytes (CMs) and non-cardiomyocytes (non-CMs) in *Ido1*$^{F/F}$ *and* *Ido1*^{mKO} mice at postnatal 3 days (P3). Four independent western blot experiments were done from four mouse per group. **b**, Ratio of heart weight/body weight at P3. **c,** CM proliferation was determined by co-immunostaining of KI67 or PH3 with TNT at P3. Bar= 50 μm. **d-f**, The cardiac structure and function in both *Ido1*$^{F/F}$ *and* *Ido1*^{mKO} mice were measured by H & E staining (**d**) and echocardiography (**e, f**) assay at P28. Bar= 1 mm in **d**. LVEF, Left ventricular ejection section. LVFS, Factional shortening. n=6/group in **b;** n=7/group in **c**, **e** and **f.** Data were expressed as mean ± SD. Statistical analysis: Student t-test assay (two-tailed) for **b, c, e** and **f**.



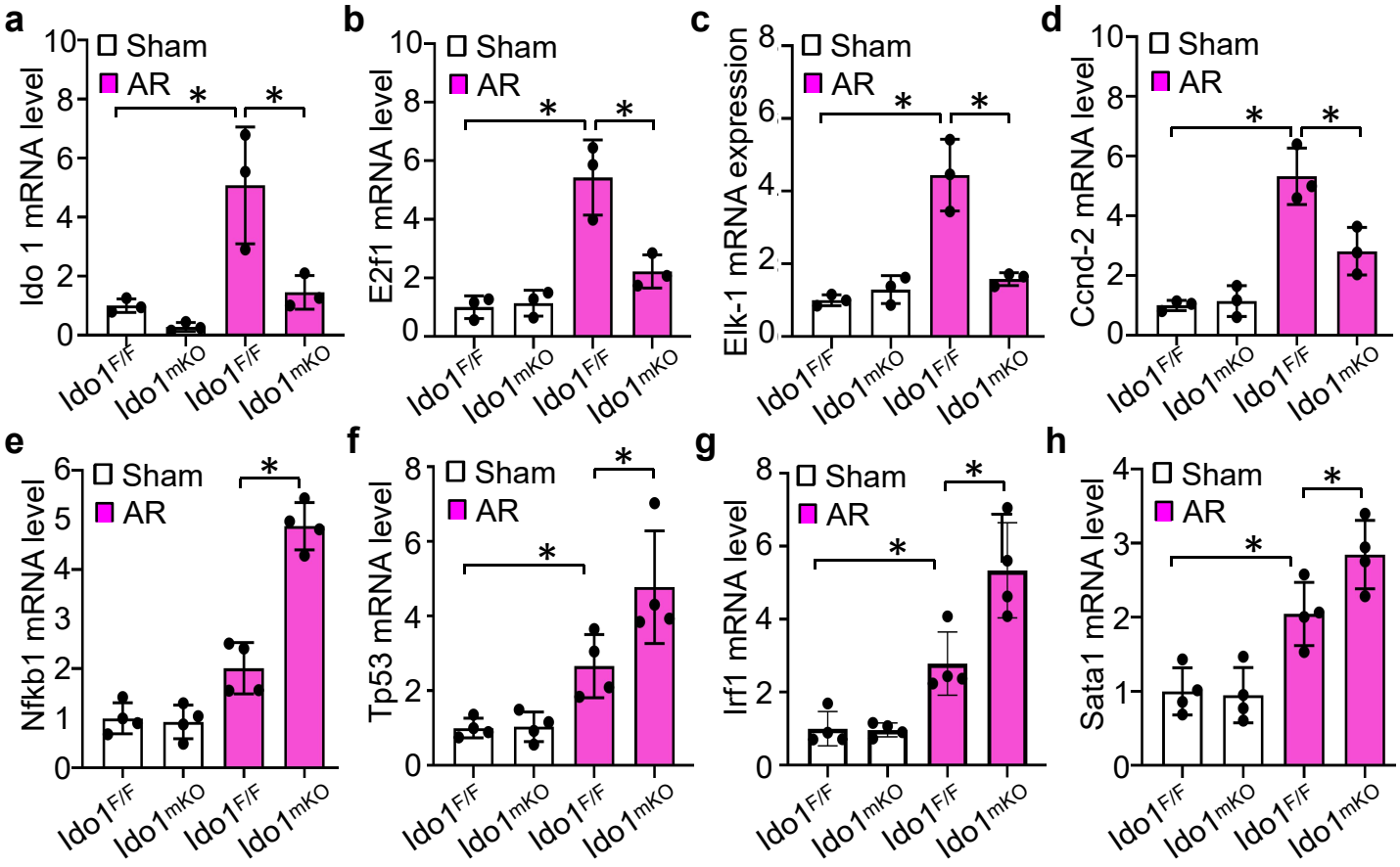
Supplementary Fig. 3. *Ido1* deletion does not induce cardiac hypertrophy and apoptosis in neonatal resected heart. *Ido1*$^{F/F}$ *and* *Ido1*^{mKO} mouse neonates were subjected to apical resection (P1) for 21 days. **a,** Wheat germ agglutinin (WGA) staining and quantification of CM cross section area. **b,** Co-Immunostaining of Tunel and TNT, and the quantifications of Tunel-positive CMs in resected hearts. Data were presented as mean ± SD (n=6/group in **a** and **b**). Bar= 50μm. Statistical analysis: one-way ANOVA followed by Tukey's multiple comparisons.



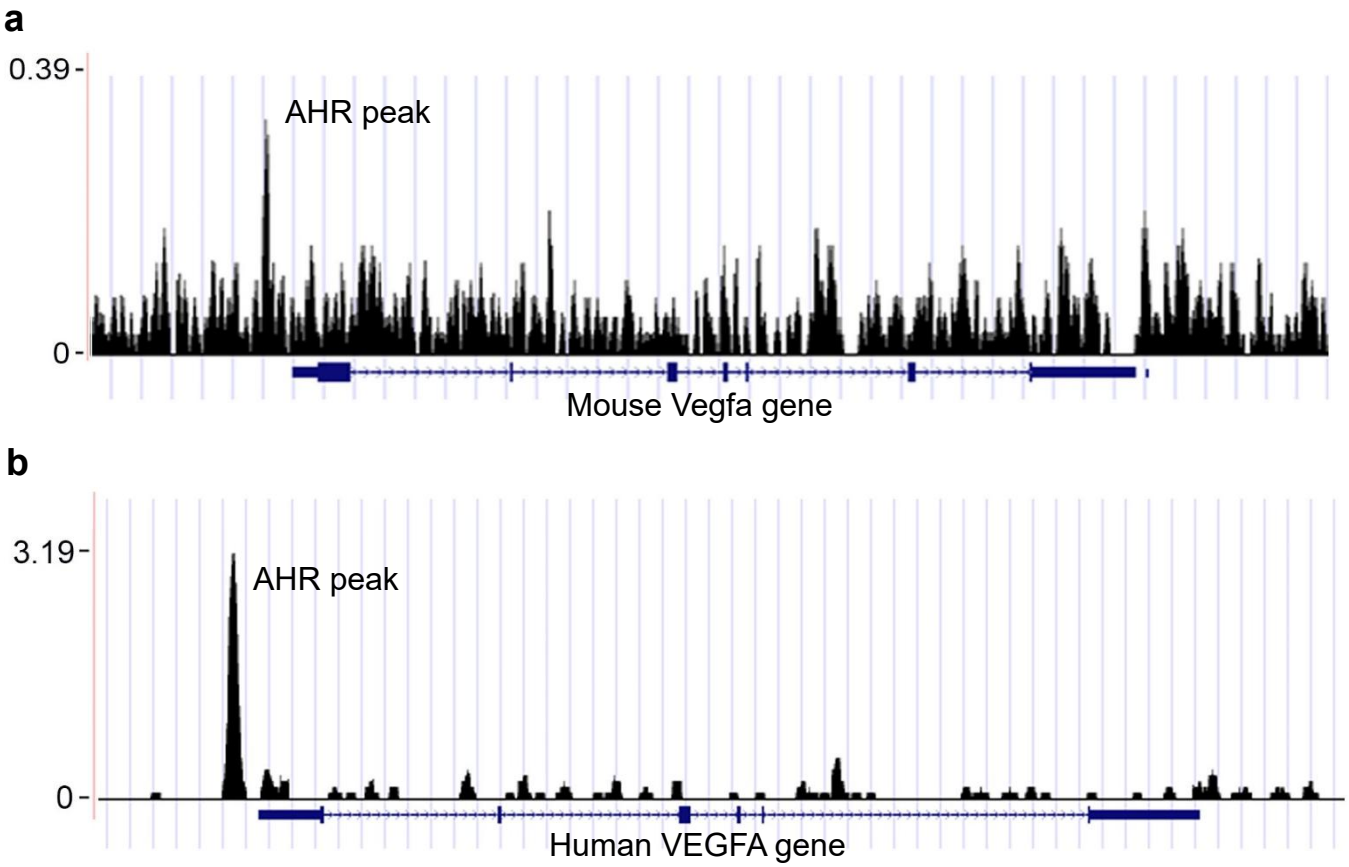
Supplementary Fig. 4. Loss of IDO in vascular smooth muscle cells (VSMC) or endothelial cells (EC) is not involved in neonatal heart regeneration. a, The strategy for studying the role of *Ido1* in VSMC or EC on neonatal heart regeneration induced by apical resection (AR) surgery. **b-c,** *Ido1* mRNA expression in VSMC (**b**) or EC (**c**) was isolated from the 7-day's regenerating heart and quantified by q-RT-PCR assay (n=3/group). **d-e,** Representative photomicrographs (**d**) and quantification (**e**) of fibrosis formation in 21-day of regenerating heart with *Ido1* deletion in VSMC or EC. Bar= 500 μm. **f-g,** Quantitative evaluation of the left ventricular ejection fraction (LVEF, **f**) and fraction section (LVFS, **g**). N=6/group for **d-g**. Values are presented as means ± SD. ***p<0.001 vs. Sham *Ido1* F/F group by one-way ANOVA followed by Tukey's multiple comparisons test in **b** and **c**. ns, no significant by one-way ANOVA assay in **e-g**.



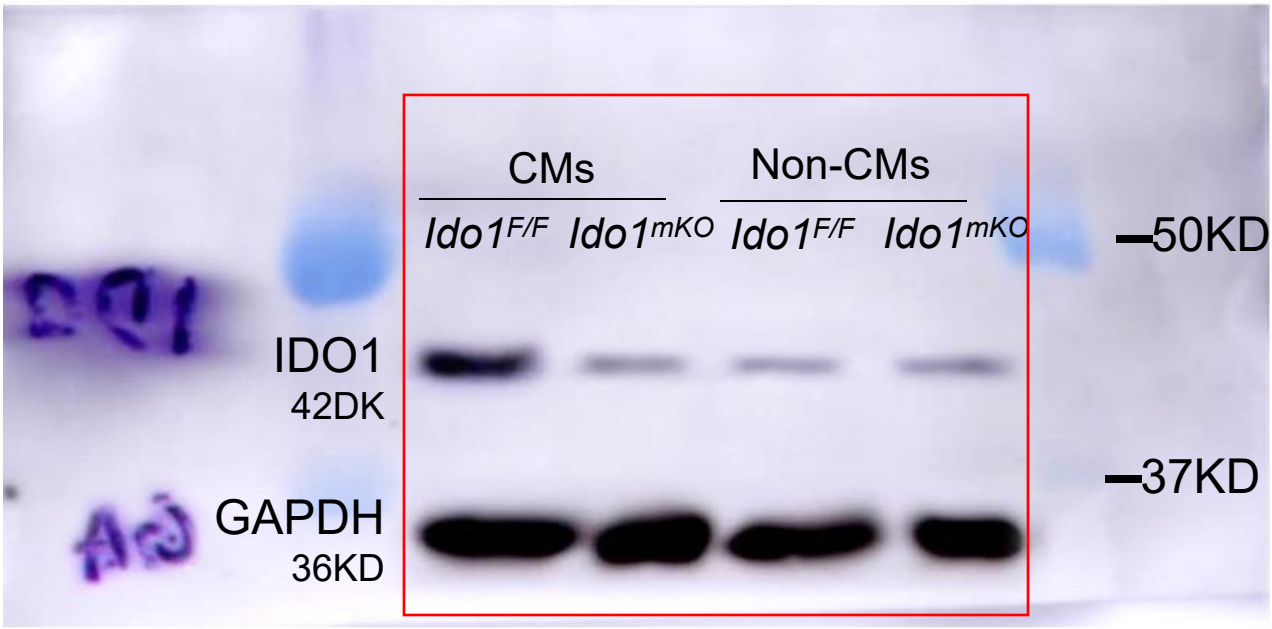
Supplementary Fig. 5. The procedure for studying the effect of Kyn on neonatal heart regeneration. a-b, WT mice were intraperitoneally (IP) injected with 100 mg/kg of 1MT (**a**) or Kyn (**b**) or PBS (Control, Ctrl) every other day from P1 up to P28 and subjected to apical resction (AR) and Sham surgery at P2 or P6, respectively. Cardiac fibrosis formation and function, and Kyn concentration were analyzed 28 days after the surgery (n= 6-8/group).



Supplementary Fig. 6. The expression of genes related to cell cycle and inflammatory pathway in neonatal heart regenerations. a-h, qRT-PCR analysis of mRNA expression at post-natal (P) 3 day after apical resection (AR) surgery at P1. n=3/group in **a-d**; n=4/group in **e-h.** Values are presented as means± SD. *p<0.05. Statistical analysis: one-way ANOVA followed by Tukey's multiple comparisons.



Supplementary Fig. 7. AHR binds to mouse and human Vegfa gene promoters. a-b, The AHR binding to the genomic VEGFA promoters in mouse liver (**a**) and human breast (**b**) cells was visualized by the UCSC Genome Browser.



Supplementary Fig. 8. Uncropped version of western blot for the Supplementary Fig. 2a.

Supplementary Table:

Supplementary Table 1. Complete list of primer sequences.

Gene	Primer sequence Forward (5'–3')	Primer sequence Reverse (5'–3')
qRT–PCR		
Ace	ATGACAAGCGACTTCTCCCC	CCAAACCGAGGACCCCATAGA
Angpt1	CACATAGGGTGCAGCAACCA	CGTCGTGTTCTGGAAGAATGA
Arid2	GAAGGCGGTAAATGGGCTTCT	TCGTTGCTAGTAGAGGACACTT
Ctnnb1	ATGGAGCCGGACAGAAAAGC	CTTGCCACTCAGGGAAGGA
Epor	GCTGGCTTAGCCCTCTCAC	CTGTCCGCTCCTAGCATGT
Fgf1	GGGCTCCGAAGAACTTCTGTG	ATGACTTTCGTGACTCACCCT
Fgf2	CTCATCCGGCAAAAGAGACAA	TTGGAGCCAAAGAGTTTGACC
Fgf9	CCAGGACAGTATAGTGGAGATCC	AGTAGACCCGCGACCCATAG
Fgfr1	ATGGCTCCCTTAGGTGAAGTT	TCCGCCTGAGAATCCCCTTT
Fgfr2	CATTGAAGCAGAAGGTACTGTGG	GGGTGGAGTTTGCACTTGATT
Gata4	GCTATAAGGTACGAAACCAGCAC	GGTTGATGGACCCGTATTCATTC
Hand2	CCCTACCCAGCCTACATGG	ACATATCGAGATTGGGGTGTCT
Hey2	GAGAACCCCTACTTCCACGG	GACAGGGCCATACTGTAGTCG
Hey2	AAGCGCCCTTGTGAGGAAAC	GGTAGTTGTCGGTGAATTGGAC
Lrp2	GAAAGCTGGACAAGACTGAGTT	GGCAGTGGTCTGTGAGAATTT
Notch1	CCCTTGCTCTGCCTAACGC	GGAGTCCTGGCATCGTTGG
Nrp1	GACAAATGTGGCGGGACCATA	TGGATTAGCCATTCACACTTCTC
Pbrm1	CTGTAGATCCTATTGCTGTGTGC	GCTTTGGAGCCCTAATGAACA
Pdgfrb	TTCCAGGAGTGATACCAGCTT	AGGGGGCGTGATGACTAGG
Prok2	GCCCCGCTACTGCTACTTC	CCGCACTGAGAGTCCTTGTC
Rxra	ATGGACACCAAACATTTCCTGC	CCAGTGGAGAGCCGATTCC
Sec24b	GGTCCAGCACAGAGTCCAATG	GGAGTCCCCGAATTTTGTGTT
Setd2	AGACTGCTGTTCCTCAGTTAAGT	CTGTATCCATTTCCGTGCTCG
Sgcd	TCCCCAACCCGATCTCTAGTG	AGGTAGTTTGATTTTCGCAGCAT
Shh	AAAGCTGACCCCTTTAGCCTA	TTCGGAGTTTCTTGTGATCTTCC
Smad6	GCAACCCCTACCACTTCAGC	GTGGCTTGTACTGGTCAGGAG
Spred1	GAGATGACTCAAGTGGTGGATG	TCTGAAAGGTAAGGCCAAACTTC
Tbx1	GTACCTGGCTTGGCACGAC	GCATTGCTGGAAACATGCG
Tgfbr1	TCTGCATTGCACTTATGCTGA	AAAGGGCGATCTAGTGATGGA
Tgfbr3	GGTGTGAACTGTCACCGATCA	GTTTAGGATGTGAACCTCCCTTG
Vegfa	GCACATAGAGAGAATGAGCTTCC	CTCCGCTCTGAACAAGGCT
Zfpm2	ACCAGGAGAGCTAGAAGTGTTT	GGACCTGAGCCTTCGTCTT
Ido1	GCTTTGCTCTACCACATCCAC	CAGGCGCTGTAACCTGTGT
Elk1	TCCTGGACCTCACGGGATG	GGGTAGGACACAAACTTGTAGAC
Myc	TTCTACGACTATGACTGCGGA	TGATGGAAGCATAATTCCTGCC
Tead2	GAAGACGAGAACGCGAAAGC	GATGAGCTGTGCCGAAGACA
Ccnb1	AAGGTGCCTGTGTGTGAACC	GTCAGCCCCATCATCTGCG
Cyp1a1	GACCCTTACAAGTATTTGGTCGT	GGTATCCAGAGCCAGTAACCT
Cyp1a2	AGTACATCTCCTTAGCCCCAG	GGTCCGGGTGGATTCTTCAG
Tp53	GTGTGGTGCAGATCGCAGT	ATCATGCCTTCGGACTTGATG
Irf1	ATGCCAATCACTCGAATGCG	TTGTATCGGCCTGTGTGAATG
Stat1	TCACAGTGGTTCGAGCTTCAG	GCAAACGAGACATCATAGGCA
Nfkb1	ATGGCAGACGATGATCCCTAC	TGTTGACAGTGGTATTTCTGGTG
Gapdh	CGACTTCAACAGCAACTCCCACTCTTCC	TGGGTGGTCCAGGGTTTCTTACTCCTT
ChIP-qPCR		
Ace	ACACCCTCTGGATTGTTCCAA	CCCTCAGCCTGAAGTTTGGT

Arid2	ACCGAGCTGACAGAGGTTTG	GTGCTTGCCTGACATTCACC
Fgfr2	ACATTCTCTGTGGAGTGCGT	GACGGAGCCTGATGAAAGGG
Gata4	GCCAGACAGGGTGGTTAGTC	AGCTCGAAGACCAAGTGCAA
Lrp1	GAAGGCCACGAATGGTCACT	GTGGTTCGTCCCTTCGTCTC
Notch1	GATTGGTCCGAGGGCATCTC	AAGCACTGGAAAGGACTCCC
Nrp1	GGAGTTCCAAAGGGTCGGAG	GCGCTGAATTGAGGCTTGTC
Rxra	AGTGACGCCTCTTTATGGCG	TGATGTCACCAACTTGCCCC
Sec24b	CCTTGTCCAGTCCCATGCTT	GAACACCTGTAACTCGCCCA
Setd2	GAAAAGGAGGGGCTGACAAGA	GTACCATTTGAGTGCAGTGCC
Spred1	ACTTGTTATGCTGCCCACGA	GTAGTCCCTCGCGACTTCTG
Smad6	AGATCAGCCGTAGACTGGGT	AAGAAGGATGGCTGCGAACA
Tgfbr3	GTGGACACTTTGCCCCTTCT	GGTGTCATCGTTTGGAGGCT
Vegfa	GCAGATCAGACAAGGGCTCA	AATGGCACGGGTCTTGGAAA