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<sup>F/F</sup> and Ido1<sup>mKO</sup> 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<sup>F/F</sup> and Ido1<sup>mKO</sup> 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*<sup>F/F</sup> and *Ido1*<sup>mKO</sup> 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. 

**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*. 

*Ido1 F/F* is the wild type, *Ido1 ecKO* is the EC-specific knockout, and *Ido1 vsmcKO* is the VSMC-specific knockout.
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 resection (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 postnatal (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   | ATGACAAGCGAAGTCTCCCC            | CCAAAACCGAGGACCCCATAGA         |
| Angpt1| CACATAGGGTGCAGCAACCA            | CGTCTGTTCTGGAGAATGA            |
| Arid2 | GAAGGCGGAATATGGCCTTCT          | TCGTTGCTAGTAGAGGACCTT          |
| Ctnnb1| ATGGACCGGAGAGAAGAAAC            | CTGGCCAATCCAGGAAAGGA           |
| Epor  | GCTGCTGAGGCCTCTACC             | CTGTCCGCTCTAGCATGT             |
| Fgf1  | GGCTCGGGAAGACTCTTGTG           | ATGACTTTGCTGACTACCT            |
| Fgf2  | CTCTCAGGAGAACACTCTCAGGC        | TTGGAGCAAAAGATTTGCC            |
| Fgf9  | CCGAGAAAGTATAGTGGGAGATCC       | AGTAGACCCGCAACCCATAG           |
| Fgrl1 | ATGTCCTGCTCTGCTTCACG           | TTGGCGCTAGAATTCCTTC            |
| Fgrl2 | CATTGAAAGCAGAAGTACTTGTG        | GGTTGAGATTTGACACTT             |
| Gata4 | GCTATAAGGAGTACAAAGCAGC         | GGTTGAGATCCGATCTGGA            |
| Hand2 | CCCTACCCAGCTCCTATGG            | ACATATCGAGATATGGGTCT           |
| Hey2  | GAGGCACCTACTCTTCCAGG           | GAGCTGGGACCTACTGTC             |
| Hey2  | AAGGCCTCTCTGGAGTTGCC           | GGTAGTTGCTGGAATTTGCC           |
| Lrp   | GAAAGCTGGAGAAAGACTCTTGG        | GCGATGTGTCTGAGAATT             |
| Notch1| CCCCTGCTCTGCACTACGG            | GAGTTGCTGCCATCTGTGG            |
| Nrp1  | GACAAATGTCGGCACGACC            | TGGATTACACATCCACCTTC           |
| Nprm1 | CTGTAATCTCTTCTCTGTC            | GCTTGGAGCCTAAATGA              |
| Pdgfrb| TTCCAGAGGTGATACACGGT           | AGGGGCCTGATGACTAG              |
| Prol  | GCCCTACTAGCTGCTGCTTC           | CCACAGCTGAGATCTCTTC            |
| Rtxa  | ATGGACACCAACACATTTCTGC         | CCAGTGGAGACCCGATCC             |
| Sec24b| GGTGCAGACTAGATGGCCCAGAT        | GGGACTCCCCCATATTTGTT            |
| Setd2 | AGACTGCGTTCTCTCAGTGG           | CTGTATCAGCCTCGGTGTC            |
| Sgcd  | TCCCCAACCGCATTCTCAGT           | AGGTAGTGTGATTCTCCGCACCAT       |
| Shh   | AAAGCTGCTCCTTACCTGCA           | TTCGAGATTTCTGATCTCTCC           |
| Smad6 | GCAAACCTTACACCTTACCA           | CTGGAGTTGACTGCTGAGGAGG         |
| Spred1| GAGATGACACCTGAGTGTGAGT         | TCTGAAGAAGTAAAGGCCAAAATCTC      |
| Tbx1  | GTACCTCAGCTGTTGCAAC            | GCTGCTGGAGAACAATCGC            |
| Tgfr1 | TCTGCAGTTAGCTTCTGTA            | AAAAGGTGGCAGTCTGAGTGGA          |
| Tgfr3 | GGTGCTGAGCTGGATGCCA            | TTGGATTAGTGTAACCTTCCGG         |
| Vegfa | GCACATAGAGAGAAAGCTTGGG         | TCTGGCTCTGAGAACAAGCT           |
| Zfp52 | ACCAGTGAAGCTAAGTGTG           | GGAATGAGCCTCGATCTCTGC           |
| Idol  | GCCTTTGCTCTACACTACCA           | CAGGGCTGTAACTGCTGT             |
| Elkl  | TCTGAGGACTACCCAGGAGT           | GGGTAGGACAAACTTTGTAGAC          |
| Myc   | TTCTACGACTATGACTTGCGGA         | TGATGGAAGCTAATTCCTGCCC         |
| Tead2 | GAAGACGAGAAGCCGAGAGG           | GATGAGCTGGTGCCGAGACA           |
| Ccnb1 | AAGGTGCTGCTGTTGCAAC            | GTACGCCCCATCATCTGGC            |
| Cypla1| GACCTTCTTCTGCTTATGGGG          | GTGTACGAGGCTGCTGAGATCT        |
| Cyplat2| AGTCATCTCTCTTACCCAGG          | GTTGGCGGTGATTCTTCTCAG          |
| Tp53  | GTGCTGAGGCAGCATGCC            | ATCATGCTGCTGAGATCTGTA          |
| Irf1  | ATGGACAAGCATGAGAC             | TTGGATCGGCCTGTTGAAT            |
| Stat1 | TCAACATGGTGGCTGACTTCA          | GCACAGGACATGCAATGGCA           |
| Nfkb1 | ATGGCAGACAGATGACCTCAC         | TTGGGACGCTGGAATCTGCT           |
| Gapdh | CGATTCAACGACACTCCCACTCCTTCC   | TGGTTGCTGAGGTGTTCTTACTCTT      |
| **ChIP-qPCR** |                               |                                 |
| Ace   | ACACCCCTGCTGTGGATCCTCA         | CCCTAGGCTGAGAATTGG             |
| Gene  | First Sequence  | Second Sequence  |
|-------|----------------|-----------------|
| Arid2 | ACCGAGCTGACAGAGGTTTG | GTGCTTGCCCTGACATTCACC |
| Fgfr2 | ACATTCTCTGTGGAGTGCTG | GACGGAGGCTGATGAAAGGG |
| Gata4 | GCCAGACAGGGTGGTTAGTC | AGCTCGAAGACCAAGTGCAA |
| Lrp1  | GAAGGCCACGAATGGTCAGT | GTGGTTCGCTCCCTTGTCCT |
| Notch1| GATTGGTCGGAGGGCATCTC | AAGCCTGGGAAGGACTCCC |
| Nrp1  | GGAGTTCCAAAGGGTGCGAG | GCGCTGAATTGAGGCTTGTC |
| Rxra  | AGTGACGCCTCTTTATGGCG | TGATGTCACCAACTTTGCCCC |
| Sec24b| CCTGTCAGTCCCCATTGCTT | GAACACCTGTAACCTGCC |
| Setd2 | GAAAAGGAGGGGTGCAAGA | GTACCATTGAGTGCAGTGCC |
| Spred1| ACTTTGTTATGCTGCCACGA | GTAGTCTCCGCGACTTTCTG |
| Smad6 | AGATCAGGGTACTGGGT | AAGAAGGATGGCTGCCAAC |
| Tgfbr3| GTGGACACTTTGCCCTTTCT | GGTGCATCGTTTGGAGGCT |
| Vegfa | GCAGATCGACACAAGGGCTCA | AATGGCACCGGTCTTGGA |

