

Supplementary Data

Figure S1. Altered expression of LRP5 in cardiomyocytes under hypoxia

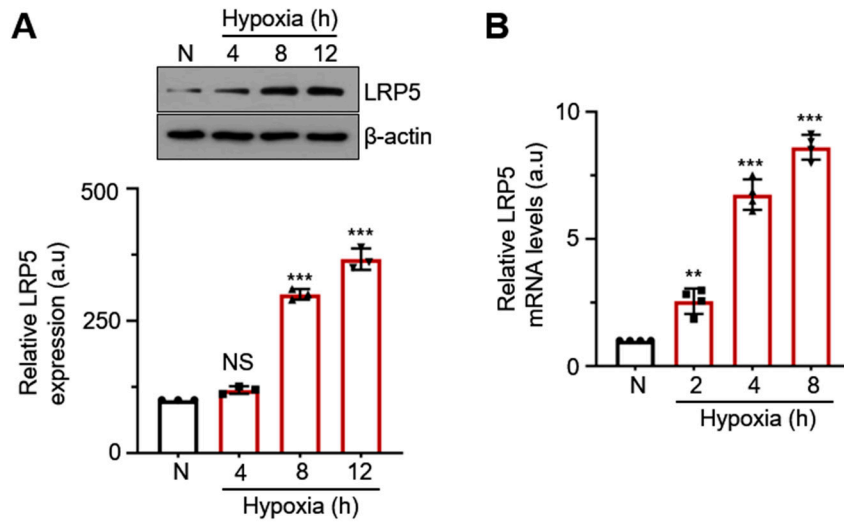


Figure S1. Cardiomyocytes were exposed to normoxia (indicated by “N”) or hypoxia (indicated by “H”) (O_2 1.2%) at the indicated times. (A) The expression levels of LRP5 were analyzed on western blotting. Protein levels were normalized to β -actin levels. $n=3$ /group. (B) The mRNA levels of LRP5 were quantified using qPCR. Gene expression was normalized to GAPDH. $n=4$ /group. All graphs show means \pm SD. ** $P < 0.01$, *** $P < 0.001$ versus Normoxia; NS, no significance.

Figure S2. Construction of LRP5/6 and shLRP5/6 adenoviral vectors and their effects on the viability of hypoxic cardiomyocytes

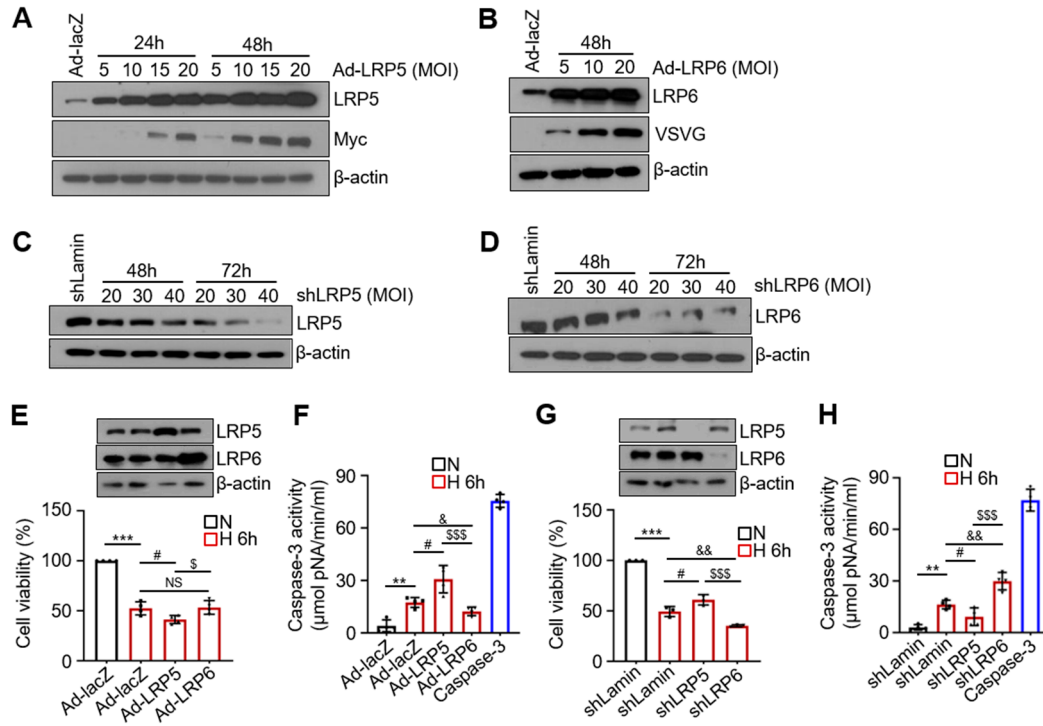


Figure S2. Cardiomyocytes were infected with adenoviruses expressing full-length LRP5/6 or shRNA targeting LRP5/6 at the indicated MOI values and times. Adenoviral transduction efficiency was assessed using western blotting. (A) Representative western blot images of cells infected with Ad-LRP5 (Myc tagging). (B) Representative western blot images of cells infected with Ad-LRP6 (VSVG tagging). (C) Representative western blot images of cells infected with shLRP5. (D) Representative western blot images of cells infected with shLRP6. Representative immunoblots from two independent experiments are presented. (E) Relative percent of cell viability was assessed using MTT assay in Ad-lacZ-, Ad-LRP5-, and Ad-LRP6-infected hypoxic cardiomyocytes. Normoxia is indicated as "N" and hypoxia is indicated as "H". Cell viability was normalized to normoxic Ad-lacZ control. n=4/group. Means \pm SD. *** P < 0.001 versus Normoxia; # P < 0.05 Ad-LRP5 versus Ad-lacZ; \$ P < 0.05 Ad-LRP6 versus Ad-LRP5; NS, no significance. (F) Measurement of caspase-3 activity for Ad-lacZ-, Ad-LRP5-, and Ad-LRP6-infected hypoxic cardiomyocytes. Data are presented in μ mol of pNA (p-Nitroaniline) per minute per volume of sample in ml. Caspase-3 was used as a positive control; 5 μ l of 5 μ g/ml. n=4/group. Means \pm SD. ** P < 0.01 versus Normoxia; # P < 0.05 Ad-LRP5 versus Ad-lacZ; \$\$\$ P < 0.001 Ad-LRP6 versus Ad-LRP5; & P < 0.05 Ad-LRP6 versus Ad-lacZ. (G) Relative percent of cell viability assessed using MTT assay in shLamin-, shLRP5-, and shLRP6-infected hypoxic cardiomyocytes. Cell viability was normalized to normoxic shLamin control. G; n=4; H; n=3. Means \pm SD. ** P < 0.01 versus Normoxia; # P < 0.05 shLRP5 versus shLamin; \$\$\$ P < 0.001 shLRP6 versus shLRP5; & P < 0.05 shLRP6 versus shLamin. (H) Measurement of caspase-3 activity for shLamin-, shLRP5-, and shLRP6-infected hypoxic cardiomyocytes. n=4/group. Means \pm SD. ** P < 0.01 versus Normoxia; # P < 0.05 shLRP5 versus shLamin; \$\$\$ P < 0.001 shLRP6 versus shLRP5; && P < 0.01 shLRP6 versus shLamin.

Figure S3. LRP5 does not regulate HIF-1 α expression at the transcriptional level but inhibits nuclear translocation of HIF-1 α

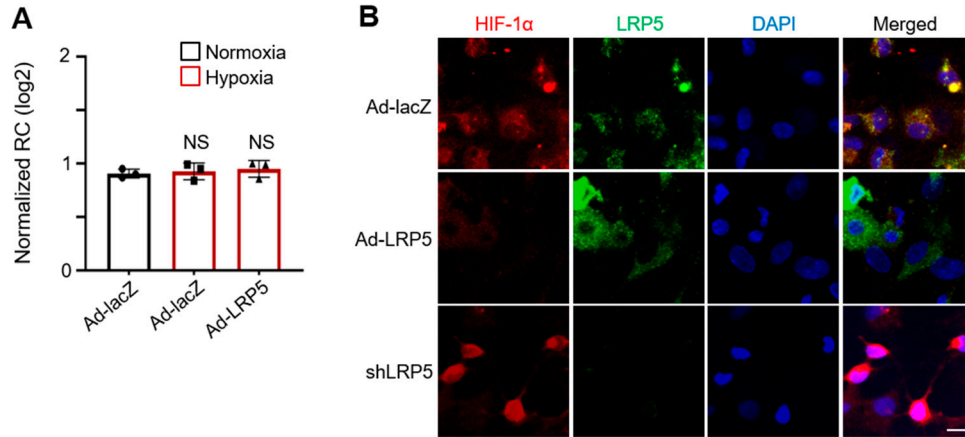


Figure S3. (A) Extracted total RNA from triplicated biological samples were subjected to mRNA sequencing. Each Fold change in hypoxic Ad-lacZ and Ad-LRP5-infected cardiomyocytes was calculated relative to normoxic Ad-lacZ control. n=3/group. Graph shows means \pm SD. NS, no significance. (B) Ad-lacZ-, Ad-LRP5-, and shLRP5-infected cardiomyocytes were co-stained with HIF-1 α (red) and LRP5 (green) after exposure to hypoxic condition (90 min). Nuclei were stained with DAPI (blue). The image shows translocation of HIF-1 α into the nucleus. Immunofluorescence was observed using confocal microscopy. Scale bar, 50 μ m.

Figure S4. Altered expression of Wnt3a in LRP5-silenced cardiomyocytes and effects of hypoxia on β -catenin expression

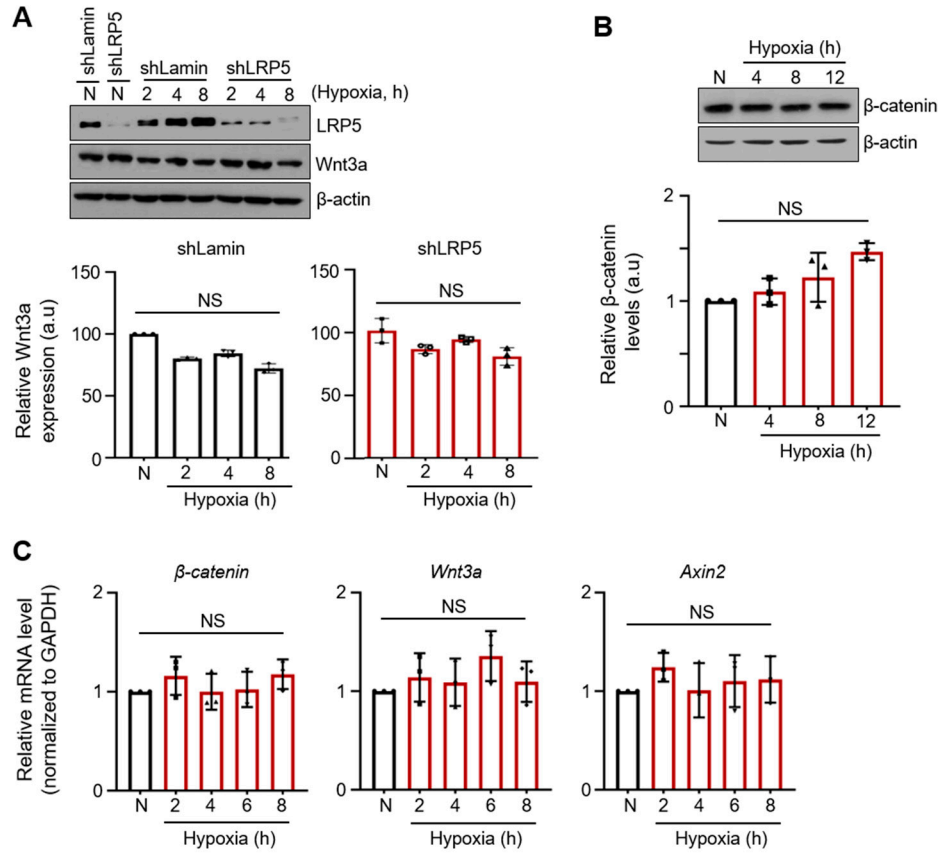


Figure S4. (A) Cardiomyocytes were exposed to normoxia or hypoxia (O_2 3%) at the indicated times. Then protein expression levels were analyzed on western blotting and their levels were normalized to β -actin levels. Protein levels were normalized to β -actin levels. $n=3$ /group. All graphs show means \pm SD. NS, no significance. **(B and C)** Cardiomyocytes were exposed to hypoxia and harvested at the indicated time points for **(B)** western blotting and **(C)** real-time qPCR. Protein and gene expression was normalized to β -actin and GAPDH, respectively. $n=3$ /group. All graphs show means \pm SD. NS, no significance.

Figure S5. *In vivo* myocardial gene delivery using adenoviruses

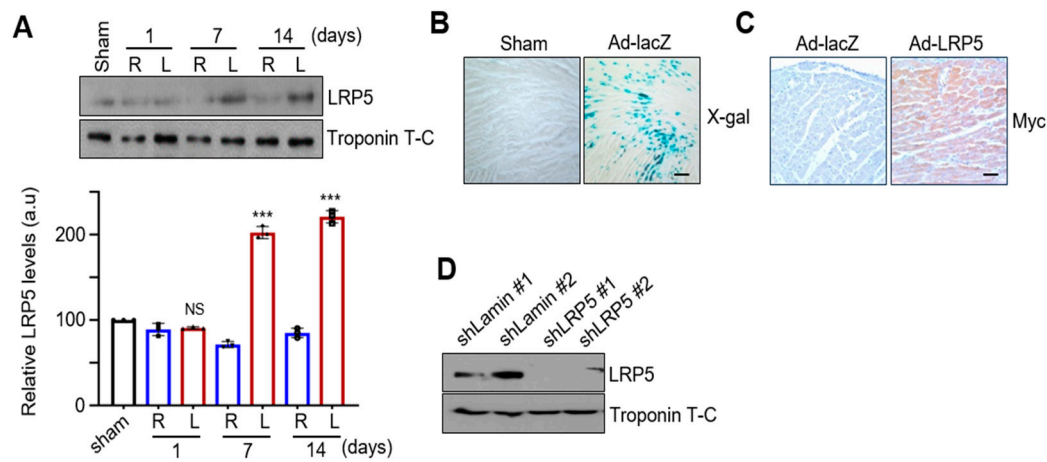


Figure S5. (A) Representative western blot analysis showing expression of LRP5 from right and left ventricle in I/R-injured heart lysates. Troponin T-C was used as the loading control. n=3/group. Graph shows means \pm SD. *** $P < 0.001$ versus right ventricle; NS, no significance. (B) Representative sections from Sham or lacZ-infected heart tissues stained with X-gal (blue) to assess β -galactosidase activity. n=3/group. Scale bar, 100 μ m. (C) Representative images of immunohistochemical staining from lacZ or LRP5-infected heart tissues using Myc antibody. n=3/group. Scale bar, 100 μ m. (D) Representative western blot analysis showing expression of LRP5 in shLamin- or shLRP5-injected heart lysates. Troponin T-C was used as the loading control.

Table S1. Functional enrichment analysis of common genes by GO-terms.

A. Ad-lacZ

Term	Category	Number of genes	%	p-value	Genes
Cellular response to hypoxia	B.P.	25	2.3	1.8E-9	Bnip3, Bnip3l, Bbc3, Fas, Higd1a, Mdm2, Ndr1, Ppargc1a, Rora, Cox4i2, Ero1a, Fam162a, Foxo3, Hmox1, IL7, Mif, Mgarp, Kcnk3, Slc2a4, Slc8a3, Stc1, Stc2, Tbl2, Vegfa, Vldlr
Response to hypoxia	B.P.	35	3.3	6.9E-9	Abcb1b, Bnip3, Cxcr4, Cx3cl1, Cbfa2t3, Cd24, Ddit4, Fosl2, Fas, Ppargc1a, Xrcc1, Aldh3a1, Aldoc, Alkbh5, Ang, Angpt2, Angptl4, Apold1, Cdkn1b, Cyp1a1, Egln1, Egln3, Ednra, Hp, Hmox1, Il1a, Il1b, Kdm3a, Nos2, Nfatc3, Ppara, Pkm, Tgfb3, Vegfa, Vldlr
Glycolytic process	B.P.	10	0.9	2.3E-5	Aldoc, Eno2, LOC100911625, Gpi, Hk2, Pfk1, Pkm, Tpi1, LOC500959, LOC100911515
Negative regulation of apoptotic process	B.P.	37	3.5	1.5E-3	Alms1, Ahi1, Bcl6, Bnip3, Bnip3l, Fas, Gli2, Higd1a, Mdm2, Mgmt, Pim1, Wt1, Amigo2, Angptl4, Alox15, Birc3, Cdkn1a, Cdkn1b, Dapk1, Ednra, Eef2k, Eif2ak2, Gnrh1, Gfer, Ifit3, Il6, Il7, Kdm2a, Ltk, Mif, Slc2a3, LOC100909595, Slc25a27, Slc40a1, Sycp2, Sycp3, Vegfa
Positive regulation of apoptotic process	B.P.	26	2.4	3.5E-3	Bcl6, Bcl2l11, Bnip3, Bnip3l, Bbc3, Bmf, Ddit3, Fas, Wt1, Aldh1a3, Dhodh, Egln1, Eif2ak2, Fam162a, Foxo3, Hmox1, Il1b, Il6, Jmy, Map3k1, Nos2, Nfatc4, Osgin1, Scin, Tfp4, Tp53inp1
Oxidation-reduction process	B.P.	43	4.0	2.8E-3	Foxred2, Hhip1, Higd1a, Ndufa4l2, Aldh1a3, Aldh1l1, Aldh3a1, Aox1, Aox2, Akr1c19, Bco1, Cbr1, Cbr3, LOC102556347, Cyp1a1, Cyp2r1, Cyp27a1, Cyp39a1, Cyp4f37, Cyp4f39, Cyp4f5, Cyp7b1, Cyb5r2, Dhrr3, Dhdh, Dhodh, Egln1, Egln3, Ero1a, Gsto2, Gfer, Hsd17b13, Kdm3a, Kdm5b, Maob, Nos2, Osgin1, P4ha2, Spr, LOC497963, RGD1560795, Smox, Srxn1
Negative regulation of transcription from RNA polymerase II promoter	B.P.	47	4.4	4.3E-3	Bcl6, Cbfa2t3, Crebrf, Ddit3, Gzfl, Gli2, Glis1, Glis3, Mxi1, Mnt, Mdm2, Phf21a, Rcor2, LOC102552640, Sox6, Sap30, Wt1, Atn1, Bhlhe40, Cbx2, Cbx7, Cdkn1c, Cpeb3, Ezh1, Efna1, Fgf9, Fnip1, Foxo3, Hist1h1c, Hdac9, Il1b, Lcor, Lpin1, Mxd1, Nfatc4, Ncoa2, Nr1d1, Ppara, Sik1, Sqstm1, Stat1, Sorbs3, Tshz2, Vegfa, Vldlr, LOC102550291, Zhx2
Apoptotic process	B.P.	23	2.1	5.0E-2	Bnip3, Bbc3, Ddit3, Ddit4, Fas, Pim1, Tnfrsf9, Wt1, XAF1, Aldoc, Birc3, Dapk1, Egln3, Foxo3, Gas2, Gja1, Irf1, Mapt, Niacr1, Rnf152, Sqstm1, Tp53inp1, Usp53
Glucose homeostasis	B.P.	12	1.1	1.3E-2	Alms1, Csmd1, Adgrf5, Foxo3, Gpi, Insr, Il6, Pde3b, Pygl, Ppp1r3g, Pdk4, Slc2a4

B. Ad-LRP5

Term	Category	Number of genes	%	p-value	Genes
Cellular response to hypoxia	B.P.	20	2.3	7.9E-8	Bnip3, Bnip3l, Bbc3, Fas, Higd1a, Mdm2, Ndrp1, Rora, Cox4i2, Ero1a, Fam162a, Foxo3, Hmox1, IL7, Mif, Mgarp, Slc8a3, Stc2, Tbl2, Vegfa
Response to hypoxia	B.P.	28	3.3	1.8E-7	Abcb1b, Bnip3, Cxcr4, Cx3cl1, Cbfa2t3, Cd24, Ddit4, Fosl2, Fas, Aldh3a1, Aldoc, Alkbh5, Angpt2, Angptl4, Apold1, Cdkn1b, Cyp1a1, Egln1, Egln3, Ednra, Hp, Hmox1, Il1a, Il1b, Kdm3a, Nos2, Tgfb3, Vegfa
Glycolytic process	B.P.	6	0.7	7.8E-3	Aldoc, Eno2, LOC100911625, Gpi, Hk2, Pfk1, Pkm, Tpi1, LOC500959, LOC100911515
Negative regulation of apoptotic process	B.P.	32	3.7	6.5E-4	Ahi1, Bcl6, Bnip3, Bnip3l, Fas, Gli2, Higd1a, Mdm2, Mgmt, Pim1, Wt1, Amigo2, Angptl4, Alox15, Birc3, Cdkn1b, Dapk1, Ednra, Eif2ak2, Gnrh1, Ifit3, Il6, Il7, Ltk, Mif, Pde3a, Slc2a3, LOC100909595, Slc25a27, Sycp2, Sycp3, Vegfa
Positive regulation of apoptotic process	B.P.	27	3.1	3.7E-5	Bcl6, Bcl2l11, Bnip3, Bnip3l, Bbc3, Bmf, Ddit3, Fas, Wt1, Aldh1a3, Dhodh, Egln1, Eif2ak2, Fam162a, Foxo3, Hmox1, Il1b, Il6, Jmy, Map3k1, Ntrk3, Ntf3, Nos2, Nfatc4, Scin, Tfp4, Tp53inp1
Oxidation-reduction process	B.P.	36	4.2	2.0E-3	Foxred2, Hhip1, Higd1a, Ndufa4l2, Aldh1a3, Aldh1l1, Aldh3a1, Aox1, Aox2, Akr1c19, Bco1, Cbr1, Cbr3, LOC102556347, Cyp1a1, Cyp2r1, Cyp27a1, Cyp39a1, Cyp4f37, Cyp4f39, Cyp4f5, Cyp7b1, Cyb5r2, Dhfr3, Dhdh, Dhodh, Egln1, Egln3, Ero1a, Gsto2, Gfer, Hsd17b13, Kdm3a, Kdm5b, Maob, Nos2, Osgin1, P4ha2, Spr, LOC497963, RGD1560795, Smox, Srxn1
Negative regulation of transcription from RNA polymerase II promoter	B.P.	37	4.3	9.6E-3	Bcl6, Cbfa2t3, Crebrf, Ddit3, Gli2, Glis1, Glis3, Mxi1, Mnt, Mdm2, Phf21a, Rcor2, LOC102552640, Wt1, Atn1, Bhlhe40, Cbx2, Cbx7, Ezh1, Efnal, Fgf9, Fnip1, Foxo3, Il1b, Lcor, Lpin1, Mxd1, Nfatc4, Ncoa2, Sik1, Sqstm1, Stat1, Sorbs3, Tshz2, Vegfa, LOC102550291, Zhx2
Apoptotic process	B.P.	20	2.3	2.7E-2	Bnip3, Bbc3, Ddit3, Ddit4, Fas, Pim1, Tnfrsf9, Wt1, XAF1, Aldoc, Birc3, Dapk1, Egln3, Foxo3, Gas2, Irf1, Niacr1, Rnf152, Sqstm1, Tp53inp1
Glucose homeostasis	B.P.	9	1.0	4.4E-2	Adgrf5, Foxo3, Gpi, Insr, Il6, Pde3b, Pygl, Ppp1r3g, Pdk4

C. shLRP5

Term	Category	Number of genes	%	p-value	Genes
Response to hypoxia	B.P.	40	3.5	7.0E-11	Abcb1b, Bnip3, Cxcr4, Cx3cl1, Cbfa2t3, Cd24, Ddit4, Fosl2, Fas, Ppargc1a, Xrcc1, Aldh3a1, Aldoc, Alkbh5, Ang, Angpt2, Angptl4, Apold1, Car9, Cdkn1b, Cyp1a1, Egln1, Egln3, Ednra, Hp, Hmox1, Kdm3a, Nos1, Nos2, Nfatc3, Ppara, Plod1, Penk, P2rx3, Pkm, Sod3, Trh, Tgfb3, Vegfa, Vldlr
Cellular response to hypoxia	B.P.	26	2.3	1.5E-9	Atp7a, Bnip3, Bnip3l, Bbc3, Fas, Higd1a, Mdm2, Ndr1, Ppargc1a, Rora, S100b, Cox4i2, Ero1a, Fam162a, Foxo3, Hmox1, Mif, LOC103694877, Mgarp, Slc2a4, Slc8a3, Stc1, Stc2, Tbl2, Vegfa, Vldlr
Oxidation-reduction process	B.P.	52	4.6	5.8E-5	Foxred2, Hhip1, Higd1a, Ndufa4l2, Aldh1a3, Aldh1l1, Aldh3a1, Aox1, Aox2, Akr1c19, Bcl6, Cbr1, Cbr3, LOC102556347, Cyp1a1, Cyp2r1, Cyp27a1, Cyp39a1, Cyp4f37, Cyp4f39, Cyp4f5, Cyp7b1, Cyb5r2, Dhfr3, Dhfr, Dhodh, Egln1, Egln3, Ero1a, Gsto2, Gfer, Hsd17b13, Kdm3a, Kdm5b, Maob, Nos2, Osgin1, P4ha2, Spr, LOC497963, RGD1560795, Smox, Srxn1
Glycolytic process	B.P.	10	0.9	4.0E-5	Aldoc, Eno2, LOC100911625, Gpi, Hk2, Pfkfb3, Pkm, Tpi1, LOC500959, LOC100911515
Negative regulation of transcription from RNA polymerase II promoter	B.P.	54	4.8	4.8E-4	Bcl6, Cbfa2t3, Creb1, Ddit3, Gatad2b, Gzfl, Gli2, Glis1, Glis3, Mxi1, Mnt, Mdm2, Phf21a, Rcor2, LOC102552640, Sox18, Sox6, Wt1, Atf1, Acvrb2, Atf1, Bhlhe40, Cbx2, Cbx7, Cdkn1c, Ednrb, Ezh1, Efn1, Fgf9, Fgf1, Foxo3, Foxp2, Hes3, LOC100912068, Hic1, Jarid2, Lcor, Lpin1, Mxd1, Msc, Mzf1, Notch1, Nfatc4, Nr0b2, Nr1d1, Ppara, Kcnip3, Rara, Sik1, Sqstm1, Sorbs3, Tshz2, Vegfa, Vldlr
Positive regulation of apoptotic process	B.P.	31	2.7	2.5E-4	Bcl6, Bcl2l1, Bnip3, Bnip3l, Bbc3, Bmf, Ddit3, Fas, S100b, Steap3, Wt1, C6, Cyp1b1, Dhodh, Egln1, Fam162a, Foxo1, Foxo3, Hmox1, Jmy, Map3k1, Map3k9, Nos2, Notch1, Nfatc4, Osgin1, Scin, Tfp4, Tp53inp1, Uaca, Zfp819
Glucose homeostasis	B.P.	15	1.3	1.1E-3	Csmd1, Adgrf5, Ankrd26, Foxo1, Foxo3, Gcgr, Gpi, Insr, Igfbp5, Pde3b, Pygl, Ppp1r3g, Pdk4, Slc2a4, Slc37a4
Negative regulation of apoptotic process	B.P.	34	3.0	2.3E-2	Ahi1, Bcl6, Bnip3, Bnip3l, Ercc5, Fas, Gli2, Higd1a, Mdm2, Wt1, Amigo2, Angptl4, Alox15, Birc3, Cdkn1b, Dapk1, Dpep1, Ednra, Ednrb, Eef2k, Foxo1, Gnrh1, Ltk, Kdm2a, Mif, Nos1, Pde3a, Pik3r1, Rara, Slc2a3, LOC100909595, Slc40a1, Syce3, Vegfa
Apoptotic process	B.P.	24	2.1	2.9E-2	Bnip3, Bbc3, Ddit3, Ddit4, Fas, Madd, Steap3, Tnfrsf9, Wt1, Aldoc, Birc3, Chik1, Dapk1, Dpep1, Duxbl1, Egln3, Foxo1, Foxo3, Gja1, Kcnip3, Rtn, Rnf153, Sqstm1, Tp53inp1

GO, gene ontology; BP, biological process.

Table S2. KEGG enrichment analysis of common genes in hypoxic cardiomyocytes.

A. Ad-lacZ

Term	Number of genes	%	p-value	Genes
Metabolic pathways	69	6.4	8.0E-3	Gbe1, Hmgcs2, Nt5c2, Gch1, Nadk2, Ndufa4l2, Rev3l, Ugp2, Ak4, Aldh1a3, Aldh3a1, Aox1, Aox2, Aldoc, Acer2, Aadat, Alox15, Bco1, Cbr1, Cbr3, LOC102556347, Cers6, Cmpk2, Cyp1a1, Cyp2r1, Cyp27a1, Cox4i2, Dhrr3, Dgki, Dhodh, Eno2, LOC100911625, Gpi, Glis2, Gfpt2, Gpat3, Hpse, Hk2, Ipmk, Kyat1, Kyat3, Lpin1, Mboat2, Maob, Mtmr14, Mtmr7, Nampt, Nos2, Olah, Pik3c2b, Pik3c2g, Phospho1, Pfk1, Pla2g2a, Pla2g4b, Pla2g6, Pla2g4f, Pla2g12a, Pygl, P4ha2, Ptges, Pdxp, Pkm, Spr, LOC497963, Tpi1, LOC500959, LOC100911515, Upp1
HIF-1 signaling pathway	40	3.6	2.5E-6	Pfkfb3, Angpt2, Cdkn1a, Cdkn1b, Egln1, Egln3, Eno2, LOC100911625, Hmox1, Hk2, Insr, Nos2, Pdk1, LOC497963, Slc2a1, Vegfa, Bnip3, Ndufa4l2, Cmpk2, Ndrgr1, Ak4, Ddit4, Ero1a, Ccng2, Maob, Angptl4, Cox4i2, Cbfa2t3, Olah, Higd1a, Fam162a, Foxo3, pdk1, Nampt, HP, Ang, Ppara, Tpi1, kyat1, Slc2a4
PI3K-Akt signaling pathway	25	2.3	4.7E-3	Bcl2l11, Ddit4, Gng4, Mdm2, Angpt2, Col6a5, Col6a6, Col11a2, Col24a1, Csf3, Cdkn1a, Cdkn1b, Efna1, Fgf11, Fgf9, Foxo3, Gys1, Insr, Il2ra, Il6, Il7, Lama5, Pdgfra, Reln, Vegfa
Cytokine-cytokine receptor interaction	21	2.0	1.3E-4	Ccl5, Cxcl10, Cxcl11, Cxcl13, Cxcl2, Cxcr4, Cx3cl1, Fas, Tnfrsf14, Tnfrsf1b, Tnfrsf9, Ackr3, Csf3, Eda2r, Il1a, Il1b, Il15ra, Il2ra, Il6, Il7, Lif
FoxO signaling pathway	14	1.3	3.1E-3	Bcl6, Bcl2l11, Bnip3, Fbxo32, Gabarapl1, Mdm2, Ccng2, Cdkn1a, Cdkn1b, Foxo3, Insr, Il6, Prkab2, Slc2a4
TNF signaling pathway	15	1.4	1.1E-4	Ccl5, Cxcl1, Cxcl10, Cxcl2, Cx3cl1, Fas, Nfkb1a, Tnfai3, Tnfrsf1b, Traf1, Birc3, Cxcl3, Il1b, Il6, Lif

B. Ad-LRP5

Term	Number of genes	%	p-value	Genes
Metabolic pathways	54	6.3	2.7E-2	Gbe1, Gch1, Nadk2, Ndufa4l2, Ak4, Aldh1a3, Aldh3a1, Aox1, Aox2, Aldoc, Acer2, Aadat, Alox15, Bco1, Cbr1, LOC102556347, Cers6, Cmpk2, Cyp1a1, Cyp27a1, Cox4i2, Dhrr3, Dgki, Dhodh, Eno2, LOC100911625, Gpi, Gfpt2, Gfpt3, Hpse, Hk2, H6pd, Ipmk, Kyat1, Lpin1, Mboat2, Maob, Mtmr14, Mtmr7, Nampt, Nos2, Olah, Pik3c2b, Pik3c2g, Pfk1, Pla2g2a, Pla2g4f, Pla2g12a, Pygl, P4ha2, Ptges, Pdxp, Spr, LOC497963
HIF-1 signaling pathway	35	4.1	7.2E-7	Pfkfb3, Angpt2, Cdkn1b, Egln1, Egln3, Eno2, LOC100911625, Hmox1, Hk2, Insr, Nos2, Pdk1, LOC497963, Slc2a1, Vegfa, Bnip3, Ndufa4l2, Cmpk2, Ndr1, Ak4, Ddit4, Ero1a, Ccng2, Maob, Angptl4, Cox4i2, Cbfa2t3, Olah, Higd1a, Fam162a, Foxo3, pdk1, Nampt, HP
PI3K-Akt signaling pathway	22	2.9	4.1E-2	Bcl2l11, Ddit4, Gng4, Mdm2, Angpt2, Col6a5, Col6a6, Col11a2, Csf3, Cdkn1b, Efna1, Fgf11, Fgf9, Foxo3, Gys1, Insr, Il2ra, Il6, Il7, Pdgfra, Reln, Vegfa
FoxO signaling pathway	11	1.3	1.2E-2	Bcl6, Bcl2l11, Bnip3, Fbxo32, Gabarapl1, Mdm2, Ccng2, Cdkn1b, Foxo3, Insr, Il6
TNF signaling pathway	14	1.6	4.1E-5	Ccl5, Cxcl10, Cxcl2, Cx3cl1, Fas, Nfkb1a, Tnfaip3, Tnfrsf1b, Traf1, Birc3, Cxcl3, IL1b, Il6, Lif
Glycolysis / Gluconeogenesis	8	0.9	6.8E-3	Aldh1a3, Aldh3a1, Aldoc, Eno2, LOC100911625, Gpi, Hk2, Pfk1

C. shLRP5

Term	Number of genes	%	p-value	Genes
Metabolic pathways	77	6.9	3.2E-4	Gbe1, Papss3, Hmgcs2, Bdh1, Nt5m, Atp6v0a4, Nadk2, Ndufa4l2, Nme3, Ugp2, Acss3, Ak4, Aldh3a1, Aox1, Aox2, Aldoc, Acer2, Aadat, Alox15, Arg1, Bco1, Cbr1, LOC102556347, Cers6, Cdo1, Cyp1a1, Cyp2r1, Cox4i2, Dhrr3, Dck, Dhodh, Eno2, LOC100911625, Gpi, Gls2, Gfpt2, Gatb, Gpat3, Hpse, Hk2, H6pd, Hykk, Hsd11b1, Itpk1, Kyat1, Lpin1, Mboat2, Maob, Mtnr14, Nampt, Nos1, Nos2, Olah, Ogdhl, Pcyt1b, Piga, Pik3c2b, Phospho1, Pfk1, Pla2g2a, Pla2g4b, Pla2g6, Pla2g4f, Pla2g12a, Ppcdc, Pygl, P4ha2, Ptgs, Ptges, Pdxp, Pkm, Spr, LOC497963, Tpi1, LOC500959, LOC100911515, Xylb
HIF-1 signaling pathway	36	3.3	7.2E-7	Pfkfb3, Mknk2, Angpt2, Cdkn1b, Egln1, Egln3, Eno2, LOC100911625, Hmox1, Hk2, Insr, Nos2, Pik3r1, Pdk1, LOC497963, Slc2a1, Vegfa, Bnip3, Ndufa4l2, Cmpk2, Ndr1, Ak4, Ddit4, Ero1a, Ccng2, Maob, Angptl4, Cox4i2, Cbfa2t3, Olah, Higd1a, Fam162a, Foxo3, pdk1, Nampt, HP
PI3K-Akt signaling pathway	24	2.1	1.3E-2	Bcl2l11, Ddit4, Gng4, Mdm2, Angpt2, Col6a5, Col6a6, Col11a2, Col24a1, Csf3, Cdkn1b, Efna1, Fgf11, Fgf9, Foxo3, Gys1, Insr, Itgb8, Il2ra, Lama5, Pik3r1, Pdgfra, Reln, Vegfa
FoxO signaling pathway	15	1.3	1.5E-3	Bcl6, Bcl2l11, Bnip3, Fbxo32, Gabarapl1, Mdm2, Ccng2, Cdkn1b, Foxo1, Foxo3, Irs3, Insr, Pik3r1, Prkab2, Slc2a4
TNF signaling pathway	10	0.9	3.6E-2	Ccl5, Cxcl2, Cx3cl1, Fas, Tab1, Tnfaip3, Traf1, Birc3, Lif, Pik3r1
Glycolysis / Gluconeogenesis	11	1.0	5.6E-4	Aldh1a3, Aldoc, Eno2, LOC100911625, Gpi, Hk2, Pfk1, Pkm, Tpi1, LOC500959, LOC100911515