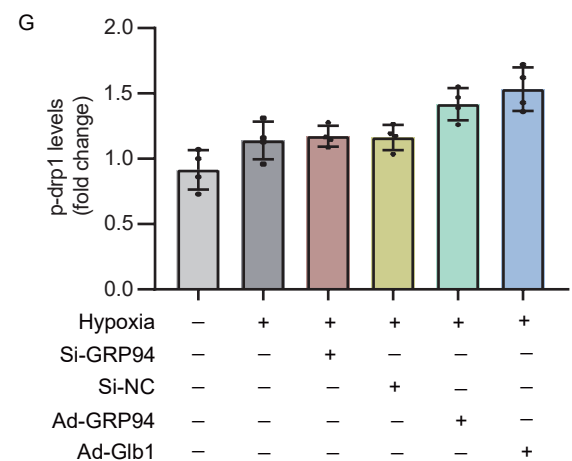
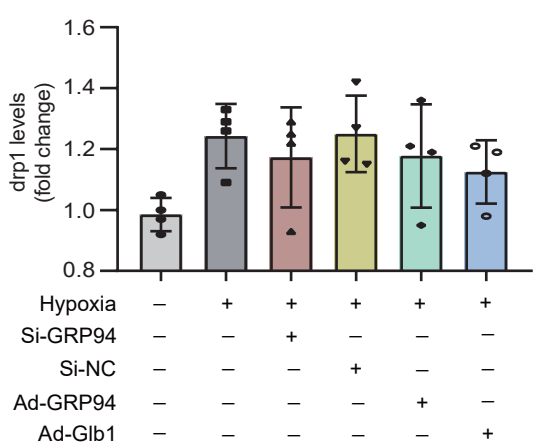
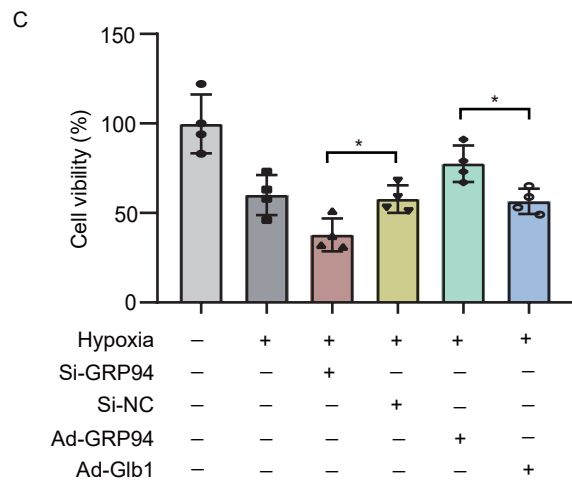
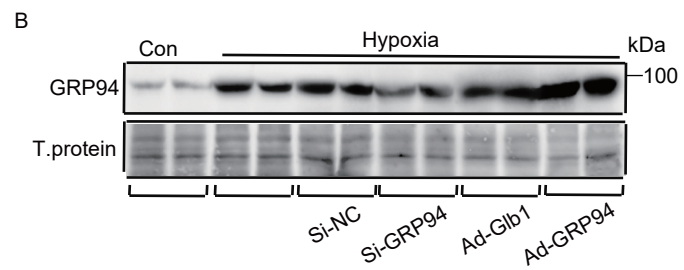
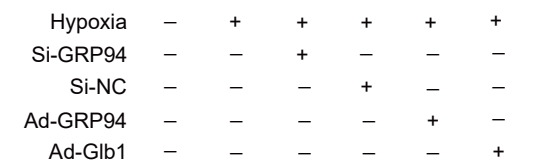
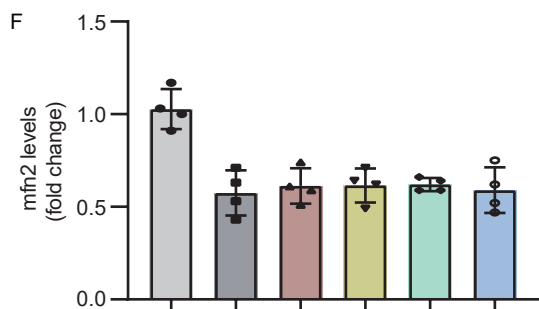
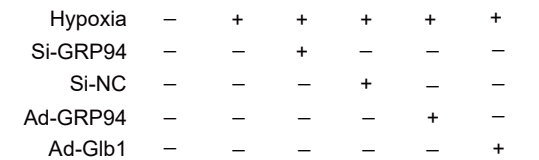
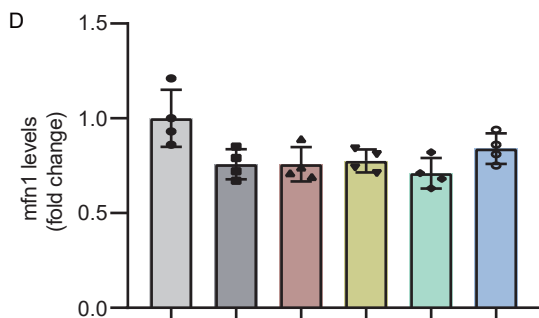
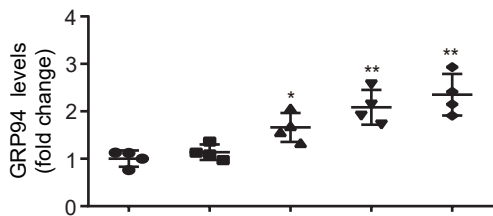
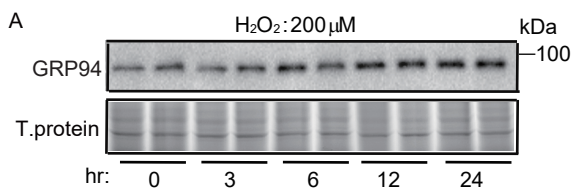
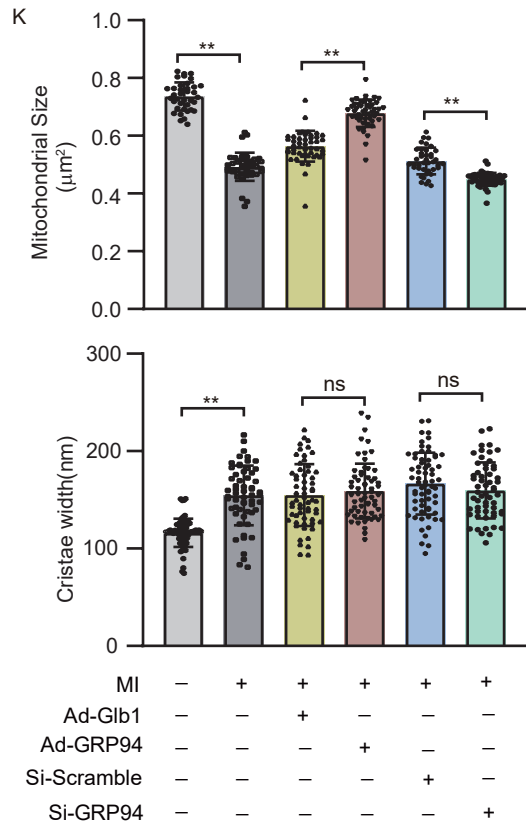
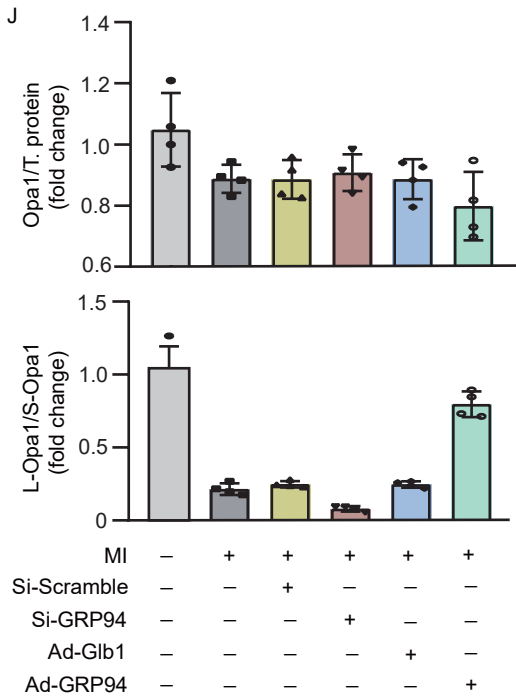
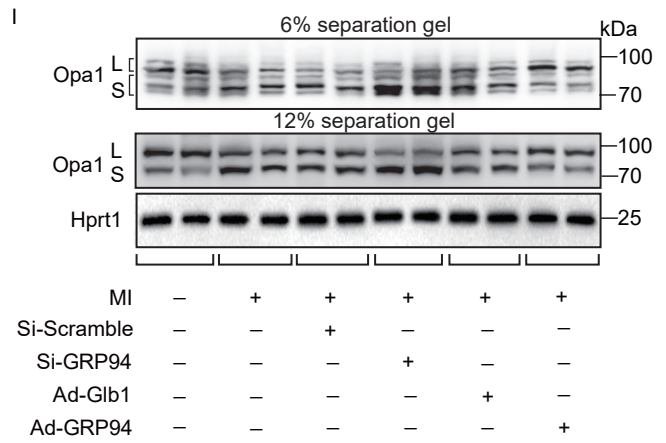
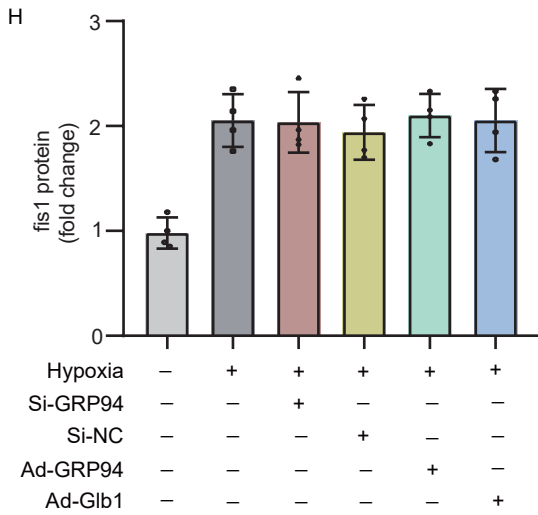
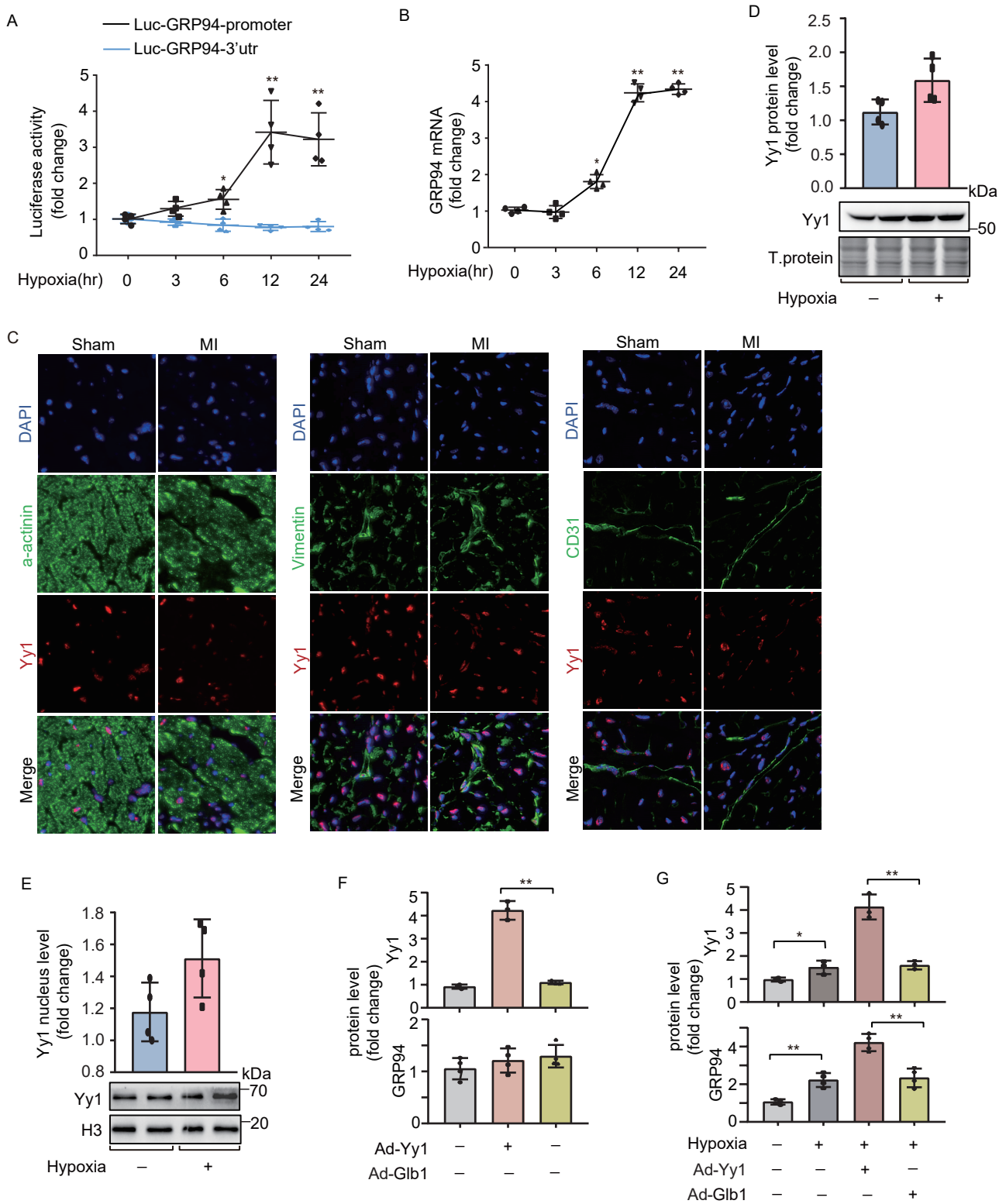


Supplementary Figure 1. Effective modulation of GRP94 levels in vivo. (A) Immunofluorescence co-staining analysis of GRP94 with cardiomyocyte marker α -actinin in mouse heart sections (scale bar: 40 μ m). The proportion of GRP94 strong signaling cells co-located with cTNT was statistically analyzed. Analysis is performed with unpaired two-tailed Student's t-test (*P<0.05, **P<0.01). (B) Immunofluorescence co-staining analysis of GRP94 with fibroblast marker Vimentin, and endothelial marker CD31 in mouse heart sections (scale bar: 40 μ m). (C-D) Adult male C57 mice (8–10 weeks old) were injected with Adeno-Associated Virus2/9-GRP94, Glb1, GRP94 siRNA, or siRNA scramble immediately after permanent left anterior descending coronary artery ligation. GRP94 levels were detected by immunoblot (n=4). *P<0.05 and **P<0.01 versus untreated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis. (E-F) GRP94 dose-dependently lowered cardiomyocyte apoptosis at 1 day post-MI. C57BL/6 mice (8-10 weeks) received intramyocardial injections of graded AAV2/9-GRP94 doses (Low: 2×10^{10} ; Medium: 1×10^{11} ; High: 2×10^{11} ; Ultra-high: 4×10^{11} viral genomes) or Ad-Glb1 control (1×10^{11} genomes) into the peri-infarct myocardium immediately after left anterior descending coronary artery ligation. Representative images show TUNEL-positive nuclei (green), DAPI counterstain (blue), and α -actinin-labeled cardiomyocytes (red; scale bar: 40 μ m; n=5). Statistical analysis used one-way ANOVA with Tukey-Kramer post hoc test (*P<0.05, **P<0.01). (G-H) GRP94 markedly improved cardiac function post-MI in a dose-dependent manner. Mice were treated as in (E), with transthoracic echocardiography performed 1 week post-MI (n=5). Left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) were analyzed by one-way ANOVA with Tukey-Kramer test (*P<0.05, **P<0.01). Data are shown as mean \pm SD.





Supplementary Figure 2. GRP94 attenuates cardiomyocyte apoptosis and mitochondrial fragmentation caused by hypoxia stress. (A) Time-dependent GRP94 degradation under oxidative stress. Cardiomyocytes treated with 200 μ M H₂O₂ for 0-24 hr. GRP94 levels analyzed by immunoblotting (n=4). *P<0.05 and **P<0.01 versus untreated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis. (B) Efficient GRP94 modulation. Cardiomyocytes infected with Ad-GRP94 or Ad-Glb1 (MOI=50, 36 hr), or transfected with GRP94 siRNA/si-NC (60 nM, 36 hr), followed by hypoxia (12 hr). GRP94 expression confirmed by immunoblotting (n=4). (C) GRP94 rescues hypoxia-induced viability loss. Cell viability assessed by CCK-8 assay under conditions in (B). *P<0.05 and **P<0.01 versus untreated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (D-H) GRP94 attenuates the cleavage of Opa1 to short (S)-Opa1 caused by hypoxia stress. Cardiomyocytes were treated as in (B). The levels of Mfn1, Mfn2, Drp1, phosphoDrp1 and Fis1 were analyzed by immunoblot. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). All data are shown as mean \pm SD. (I-J) GRP94 attenuates the cleavage of Opa1 to short (S)-Opa1 caused by MI. Adult male C57 mice (8–10 weeks old) were injected with Adeno-Associated Virus2/9-GRP94, Glb1, GRP94 siRNA or siRNA scramble and subjected to permanent left anterior descending coronary artery ligation. The levels of Opa1 were analyzed by immunoblot with Hprt1 as internal control (n=4). *P<0.05 and **P<0.01 in one-way ANOVA followed by Tukey–Kramer post hoc analysis. (K), Quantification of mean mitochondrial size (the upper). n=37 for sham group, 43 for MI, 47 for Ad-Glb1, 49 for Ad-GRP94, 41 for Si-Scramble, and 53 for Si-GRP94. Quantification of cristae width (below). n=70 for sham group, 58 for MI, 60 for Ad-Glb1, 63 for Ad-GRP94, 66 for Si-Scramble and 58 for Si-GRP94. Analysis was performed with one-way ANOVA followed by Tukey–Kramer post hoc analysis. *P<0.05; **P<0.01. ns, no significance.



H

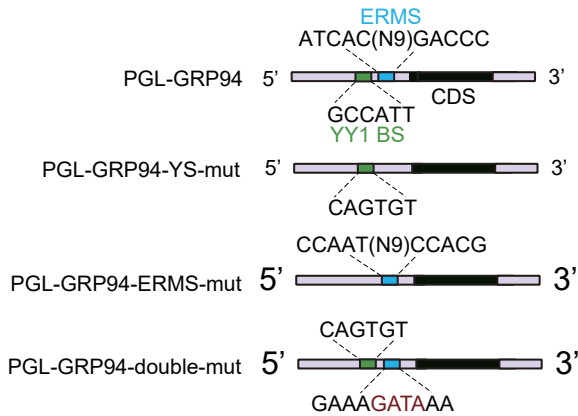
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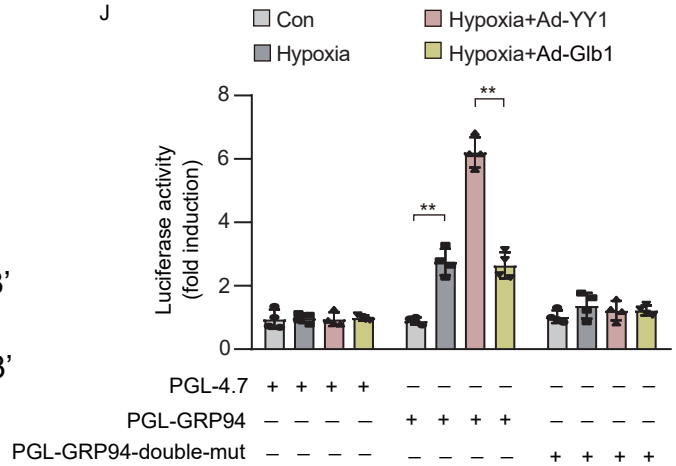
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Yy1 BS ERMS

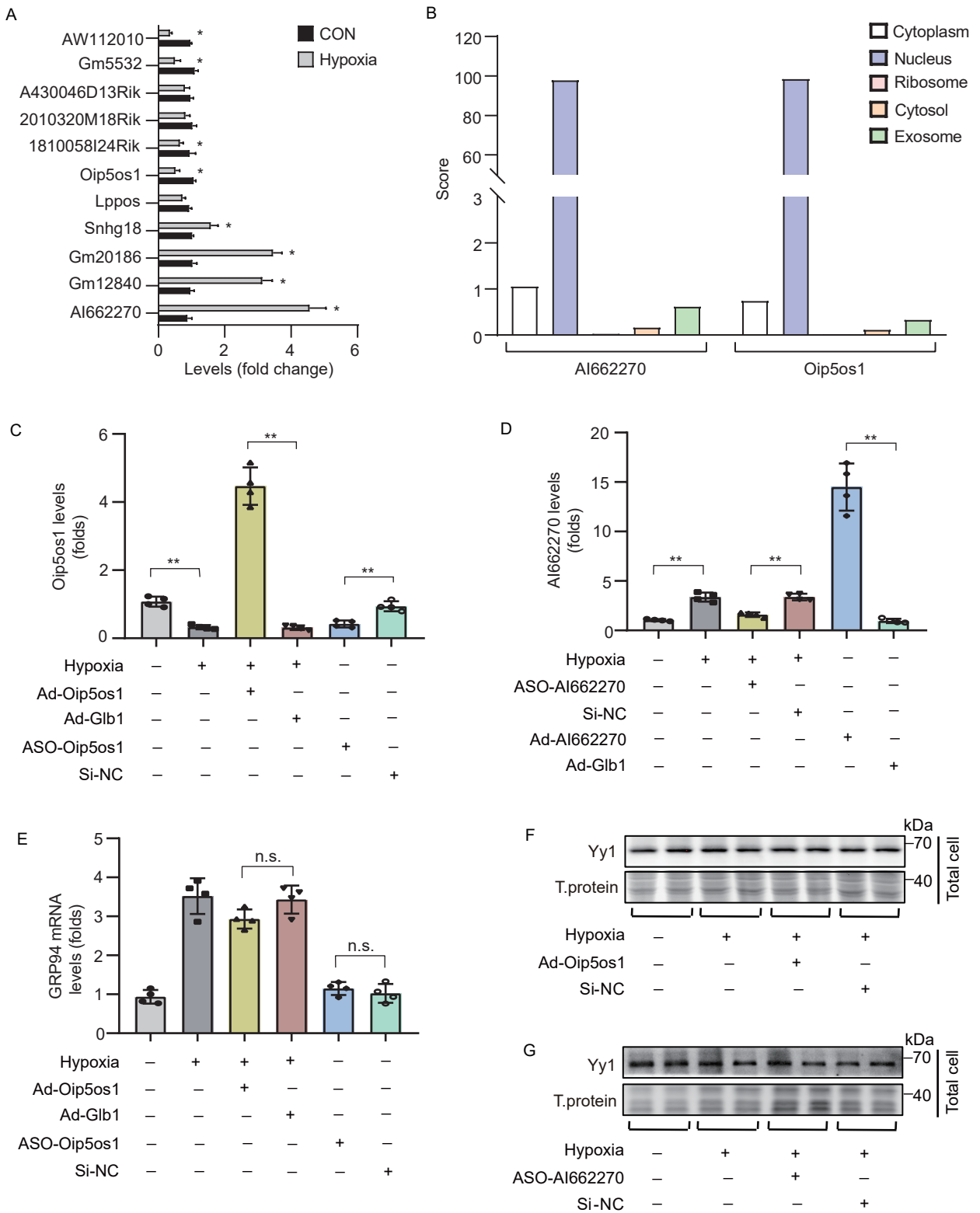
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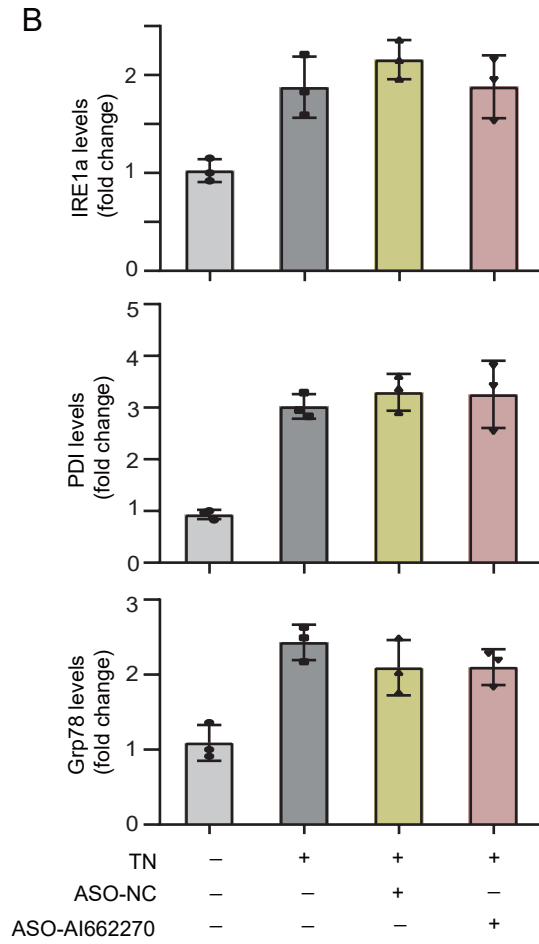
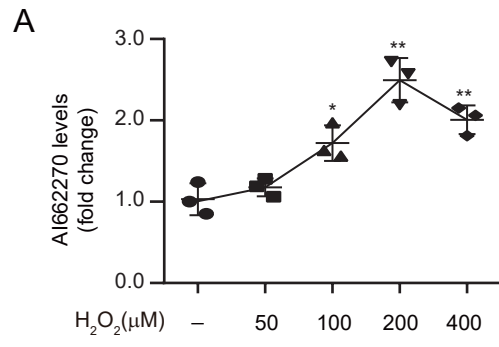
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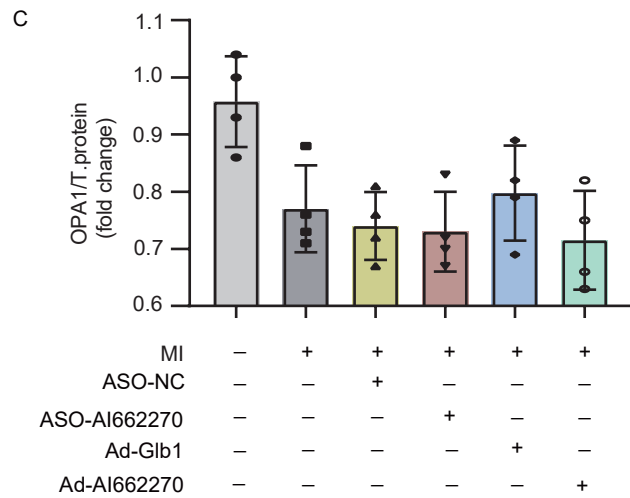
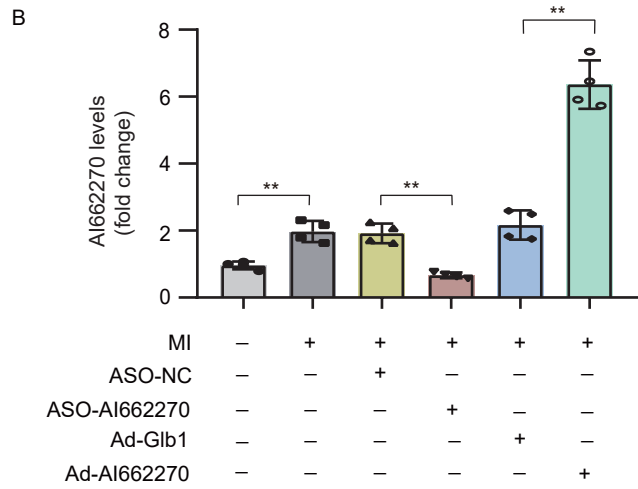
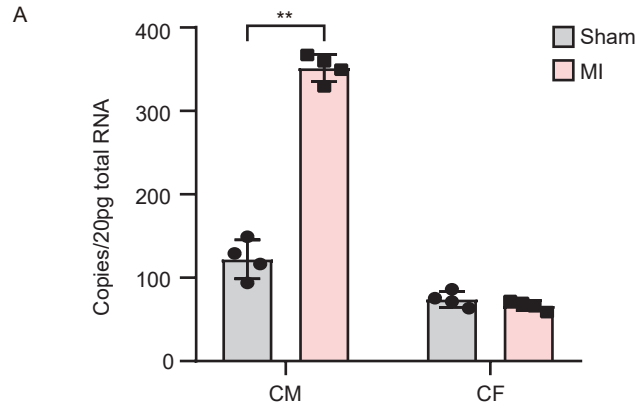
Supplementary Figure 3. Yy1 transcriptionally regulates GRP94 under hypoxia through conserved promoter elements. (A) Hypoxia enhances GRP94 promoter activity. MCM cell lines were transfected with the constructs of the pGL-4.17 empty vector (pGL-4.17) or the pGL-4.17 vector harboring GRP94 promoter (pGL-GRP94) at 1ng/ml. After 24h, cells were cultivated for another 12h under hypoxic conditions. Luciferase activity was assayed. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (B) Hypoxia induces an increase of GRP94 mRNA. Cardiomyocytes under hypoxia (0-24 hr). GRP94 mRNA quantified by qRT-PCR. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (C) Immunofluorescence co-staining analysis of Yy1 with cardiomyocyte marker α -actinin, fibroblast marker Vimentin, and endothelial marker CD31 in mouse heart sections (scale bar: 40 μ m). (D) Hypoxia has no significant effect on Yy1 protein level. Cardiomyocytes were cultivated under hypoxia for 12 hr. Yy1 protein was then analyzed by immunoblot (n=4). Analysis is performed with an unpaired two-tailed Student's t-test. (E) Hypoxia has no significant effect on Yy1 nuclear localization. Cardiomyocytes were cultivated under hypoxia for 12 hr. Nucleuses were isolated, and Yy1 protein was then analyzed by immunoblot (n=4). Analysis is performed with an unpaired two-tailed Student's t-test. (F-G) AI662270 or Oip5os1 does not affect Yy1 nuclear content. Cardiomyocytes were infected with Ad-Oip5os1 (MOI=40) or transfected with ASO-AI662270 (40 nM, 36 hr) prior to hypoxia. Nuclear fractionation was isolated, and Yy1 protein was then analyzed by immunoblot. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (H) Alignment analysis of the mouse, rat and human GRP94 promoter pairs. The conserved ERSE motif (boxed) and adjacent Yy1 binding site (underlined) are indicated in bold letters with an underline. (I) Mutated GRP94 promoter in the Yy1 binding site and/or ERMS are shown. (J) Dual mutation of ERMS/Yy1 sites abolishes Yy1-mediated promoter activation. MCM were transfected with the constructs of the pGL-4.17 empty vector (pGL-4.17), the pGL-4.17 vector harboring GRP94 promoter (pGL-GRP94) or the promoter with dual mutations in the ERMS and Yy1 binding site (pGL-GRP94-double-mut) respectively at 1ng/ml and then infected with the adenoviral Glb1 or Yy1 at 40 MOIs. After 24h, cells were cultivated for 12h under hypoxic conditions. Luciferase activity was assayed. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). All data are shown as mean \pm SD.



Supplementary Figure 4. LncRNA-AI662270 interacts with Yy1 to promote GRP94 transcription. (A) The differentially expressed LncRNAs in the mouse model post-MI were confirmed by qRT-PCR. Cardiomyocytes were cultivated for 12h under hypoxic conditions. *P<0.05 and **P<0.01 versus the control group in Student's t-test (n=3). (B) Subcellular localization prediction of AI662270 and Oip5os1. (C) Oip5os1 modulation in cardiomyocytes. Adenoviral overexpression (Ad-Oip5os1 vs. Ad-Glb1 at MOI 40) or ASO-mediated knockdown (40 nM ASO-Oip5os1 vs. ASO-NC) followed by 12 h hypoxia. qRT-PCR quantification (n=4). *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (D) AI662270 modulation using adenoviral overexpression (Ad-AI662270) or ASO knockdown under identical experimental conditions as panel C. (E) Lnc-Oip5os1 shows no effect on the mRNA level of GRP94. Experimental setup as panel C. The mRNA of GRP94 was then analyzed by qRT-PCR. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=4). (F-G) AI662270 or Oip5os1 does not affect the total Yy1 content. Cardiomyocytes were infected with adenoviruses overexpressing Oip5os1 (Ad-Oip5os1) or Glb1 (Ad-Glb1) at MOIs of 40, or transfected with 40nM ASO-AI662270 or ASO-NC. After 36h, cells were cultivated for 12h under hypoxic conditions. Yy1 protein was then analyzed by immunoblot. All data are shown as mean ± SD.

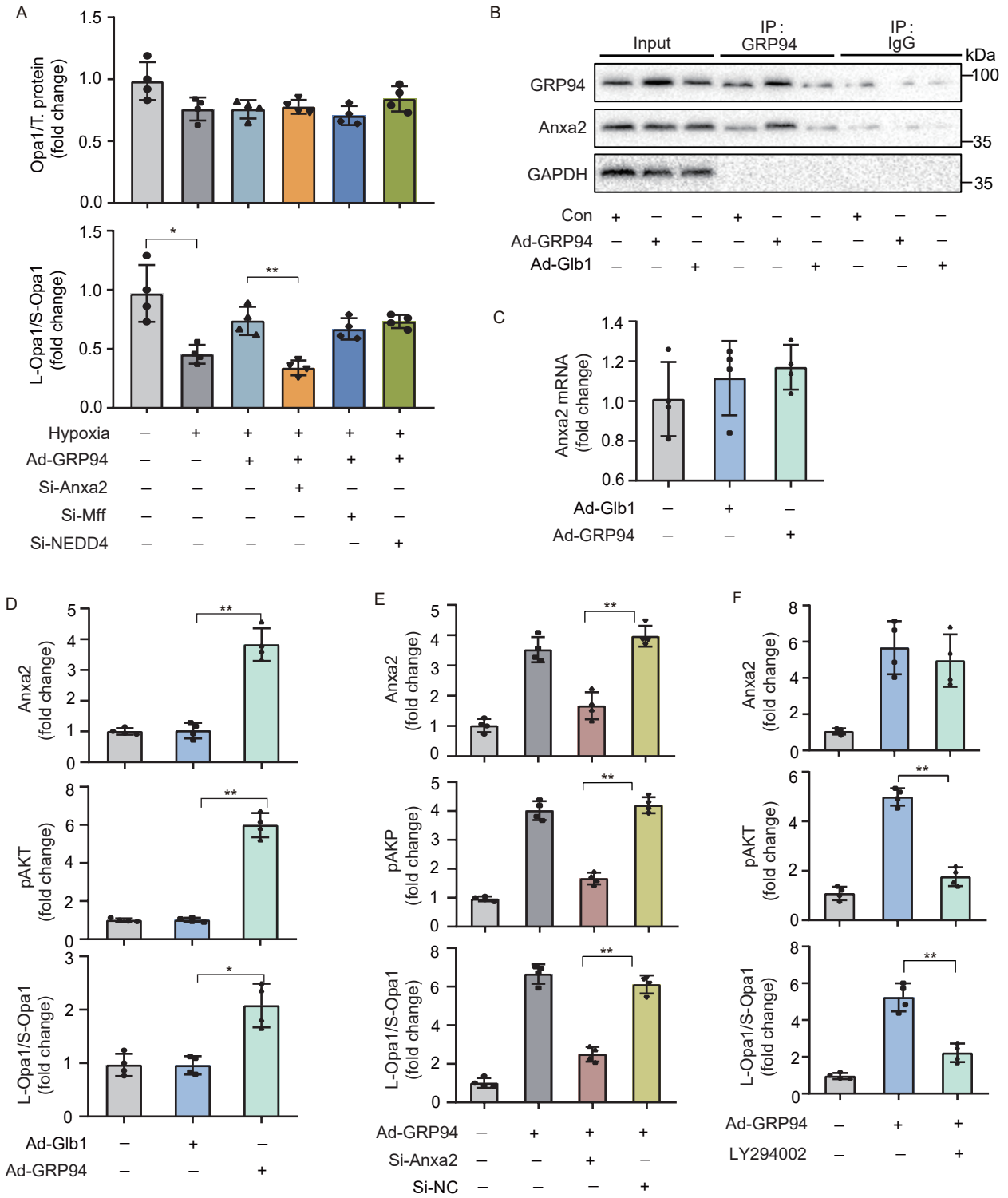


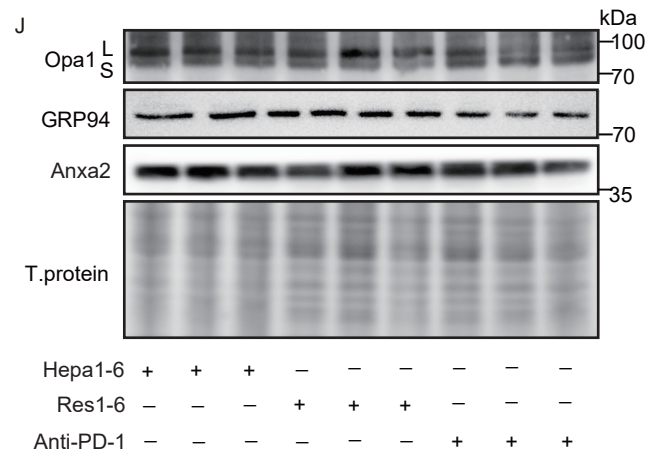
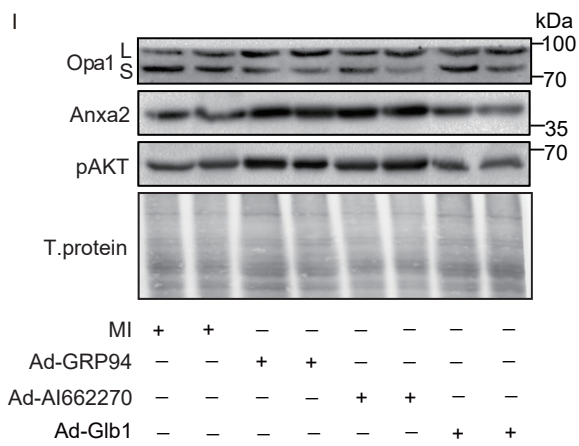
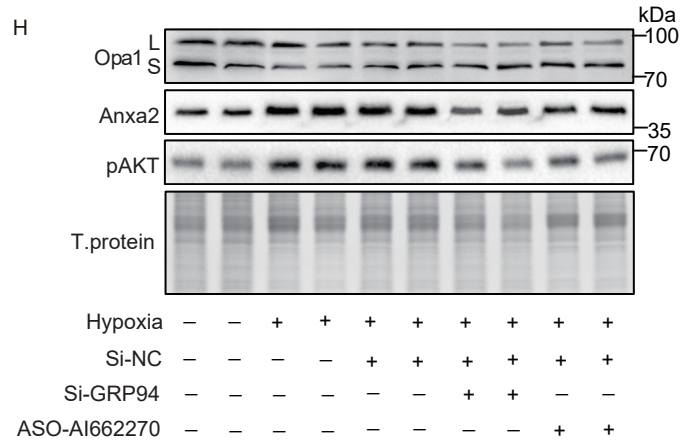
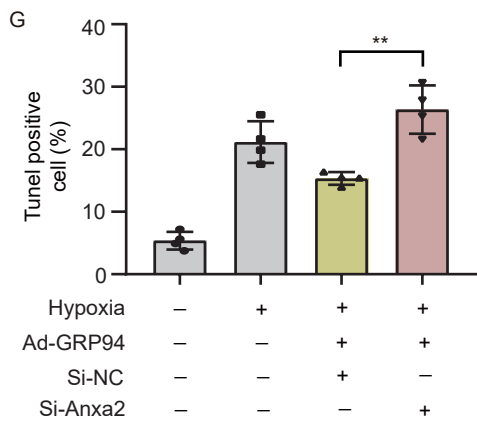
Supplementary Figure 5. ER stress-induced LncRNA-AI662270 exerts GRP94-like functional effects in vitro. (A) H₂O₂ treatment induces an increase in AI662270 levels. Cardiomyocytes were treated with the indicated dose of H₂O₂ for 12h. AI662270 levels were analyzed by qRT-PCR (n=3). Analysis was performed with one-way ANOVA followed by Tukey–Kramer post hoc analysis. *P<0.05, **P<0.01. (B) AI662270 knockdown attenuates ER stress signaling. Cardiomyocytes transfected with 40 nM ASO-AI662270 or ASO-NC for 24 h, followed by tunicamycin (TN, 15 mg/L) challenge for 12 h. Immunoblot analysis of ER stress markers (IRE1 α , PDI, GRP78). Analysis was performed with one-way ANOVA followed by Tukey–Kramer post hoc analysis (n=3). All data are shown as mean \pm SD.



Supplementary Figure 6. Lnc-AI662270 exerts cardioprotective effects post-MI.

(A) Absolute quantitative real-time PCR analysis of AI662270 expressions in cardiomyocytes and cardiac fibroblasts isolated from Sham and MI groups (n=4). *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis. (B) Manipulation of AI662270 levels in the mouse model. Adult male C57 mice (8–10 weeks old) were injected with Adeno-Associated Virus2/9-AI662270, Glb1, ASO-AI662270, or ASO-NC immediately after permanent left anterior descending coronary artery ligation. AI662270 levels were analyzed by qRT-PCR (n=4). (C) AI662270 does not influence total Opa1 protein levels. Mice were treated as in (A). Opa1 protein was analyzed by immunoblot. All data are shown as mean ± SD. *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis.





Supplementary Figure 7. GRP94 interacts with Anxa2 to modulate Opa1 proteolytic processing. (A) Anxa2 ablation abrogates GRP94-mediated effects on Opa1 processing. Cardiomyocytes were co-transfected with 40 nM siRNA targeting Anxa2 (Si-Anxa2), Mff (Si-Mff), NEDD4 (Si-Nedd4), or siRNA scramble (Si-NC), followed by adenoviral infection (MOI=50) expressing GRP94 (Ad-GRP94) or β -galactosidase (Ad-Glb1). After 36 h, cells were exposed to hypoxia (1% O₂) for 12 h. Opa1 protein was analyzed by immunoblot. (B) Endogenous GRP94-Anxa2 interaction. Co-immunoprecipitation (Co-IP) using GRP94 antibody or IgG control in cardiomyocytes treated with 15 mg/L tunicamycin for 12 h. (C) GRP94 overexpression does not alter Anxa2 transcript levels. qRT-PCR analysis 48 h post-Ad-GRP94/Ad-Glb1 infection (n=4). (D) GRP94 enhances Anxa2 protein stabilization. Western blot analysis of Anxa2, p-AKT (Ser473), and Opa1 isoforms after 48 hr adenovirus overexpressing GRP94 (Ad-GRP94) or Glb1 (Ad-Glb1) at MOIs of 50 infection (n=4). (E) Anxa2 knockdown reverses GRP94-induced AKT phosphorylation and Opa1 processing. Immunoblot analysis following Ad-GRP94 infection (MOI=50) with Si-Anxa2/Si-NC (40nM). (F) AKT inhibition blocks GRP94-mediated effects. LY294002 (50 μ M, 48h) treatment with Ad-GRP94 infection (MOI=50). (G) Anxa2 deletion abolishes the protective effect of GRP94 on hypoxia-induced apoptosis. TUNEL assay quantification (n=4). (H) AI662270 knockdown represses hypoxia-induced Anxa2 as GRP94 deletion did. Western blot analysis after 60 nM Si-GRP94 or 40 nM ASO-AI662270 transfection with 12h hypoxia (n=3). (I) AI662270 augments the levels of L-Opa1, Anxa2, and phosphorylated AKT in the mouse model as GRP94 does. C57BL/6 mice (8-10 weeks) received AAV2/9-GRP94, AAV2/9-AI662270, or AAV2/9-Glb1 immediately after permanent LAD ligation. Opa1, Anxa2, and phosphorylated AKT protein were analyzed by immunoblot (n=3). (J) Anti-PD-1 treatment decreases the cardiac level of GRP94/L-Opa1 signal. For metastasis challenge experiments, mice were injected with Hepa1-6 cells or drug-resistant Hepa1-6 cells (termed as Res1-6). After tumor formation, mice were treated with 200 μ g of PD-1 antibody (anti-PD-1) three times a week for two weeks. Cardiac protein levels analyzed by western blot (n=3). *P<0.05 and **P<0.01 versus the indicated group in one-way ANOVA followed by Tukey–Kramer post hoc analysis. All data are shown as mean \pm SD.

Supplementary Table 1: RNA deep sequencing results revealed the extensive alteration of cardiac ER stress-response genes at 1d and 7d post MI in mice model.

| Official_Symbol | Gene type | Mean_Sham | Mean_MI1d | Mean_MI7d | Folds (MI1d/Sham) | Folds (MI7d/Sham) | pValue (MI1d/Sham) | pValue (MI1d/S ham) | pValue (MI7d/MI1d) |
|-----------------|----------------|-----------|-----------|-----------|-------------------|-------------------|--------------------|---------------------|--------------------|
| Ddit3 | protein_coding | 43.82 | 14.20 | 16.43 | 0.32 | 0.38 | 0.08 | 0.09 | 0.02 |
| Ppp1r15a | protein_coding | 14.80 | 10.27 | 10.06 | 0.69 | 0.68 | 0.03 | 0.05 | 0.91 |
| Atf6 | protein_coding | 23.43 | 22.54 | 16.69 | 0.96 | 0.71 | 0.62 | 0.02 | 0.01 |
| Atf4 | protein_coding | 40.59 | 40.88 | 35.40 | 1.01 | 0.87 | 0.97 | 0.44 | 0.40 |
| Atf3 | protein_coding | 6.69 | 7.83 | 4.25 | 1.17 | 0.63 | 0.65 | 0.11 | 0.14 |
| Ern2 | protein_coding | 4.13 | 4.33 | 4.35 | 1.05 | 1.05 | 0.49 | 0.48 | 0.97 |
| Hspa5 | protein_coding | 23.15 | 35.98 | 25.88 | 1.55 | 1.12 | 0.01 | 0.23 | 0.03 |
| Canx | protein_coding | 3.26 | 3.39 | 3.02 | 1.04 | 0.93 | 0.78 | 0.55 | 0.44 |
| Ero1l | protein_coding | 7.21 | 9.42 | 6.70 | 1.31 | 0.93 | 0.12 | 0.42 | 0.06 |
| Xbp1 | protein_coding | 1.88 | 2.67 | 2.02 | 1.42 | 1.08 | 0.03 | 0.54 | 0.01 |
| Erp44 | protein_coding | 17.38 | 21.68 | 17.21 | 1.25 | 0.99 | 0.00 | 0.86 | 0.01 |
| Hsp90b1 | protein_coding | 231.31 | 384.54 | 228.20 | 1.66 | 0.99 | 0.00 | 0.76 | 0.00 |
| Calr | protein_coding | 201.44 | 358.78 | 213.59 | 1.78 | 1.06 | 0.00 | 0.44 | 0.00 |
| Edem1 | protein_coding | 6.07 | 12.28 | 11.00 | 2.02 | 1.81 | 0.00 | 0.03 | 0.47 |
| Dnajc3 | protein_coding | 17.54 | 28.02 | 22.40 | 1.60 | 1.28 | 0.00 | 0.09 | 0.08 |
| Pdia3 | protein_coding | 89.04 | 188.07 | 126.44 | 2.11 | 1.42 | 0.00 | 0.02 | 0.01 |
| Pdia4 | protein_coding | 24.59 | 64.15 | 39.15 | 2.61 | 1.59 | 0.00 | 0.00 | 0.00 |

Supplementary Table 2: The differently expressed LncRNAs in left ventricular myocardium, with the multiple of expression level change less than 0.7 or more than 1.5 and p value less than 0.05, at 1d and 7d post MI in mice model.

| Official_Symbol | Gene type | Mean_Sham | Mean_MI1d | Mean_MI7d | Folds (MI1d/Sham) | Folds (MI7d/Sham) | pValue (MI1d/Sham) | pValue (MI1d/S ham)2 | pValue (MI7d/MI1d) |
|----------------------|-----------|-----------|-----------|-----------|-------------------|-------------------|--------------------|----------------------|--------------------|
| AI662270 | lincRNA | 3.21 | 11.74 | 5.00 | 3.66 | 1.56 | 0.00 | 0.26 | 0.02 |
| Gm12840 | lincRNA | 131.93 | 319.09 | 264.96 | 2.42 | 2.01 | 0.00 | 0.00 | 0.11 |
| Gm20186 | lincRNA | 17.22 | 36.27 | 36.79 | 2.11 | 2.14 | 0.03 | 0.00 | 0.93 |
| Hist2h2bb | lincRNA | 3.38 | 6.83 | 6.69 | 2.02 | 1.98 | 0.00 | 0.08 | 0.92 |
| Gm26857 | lincRNA | 2.58 | 4.89 | 3.17 | 1.90 | 1.23 | 0.01 | 0.07 | 0.03 |
| Gm26882 | lincRNA | 1.43 | 2.46 | 1.89 | 1.72 | 1.33 | 0.00 | 0.16 | 0.14 |
| Lppos | lincRNA | 4.59 | 3.17 | 3.79 | 0.69 | 0.83 | 0.01 | 0.08 | 0.06 |
| 1700020I14Rik | lincRNA | 55.12 | 37.36 | 37.96 | 0.68 | 0.69 | 0.02 | 0.02 | 0.84 |
| 1810058I24Rik | lincRNA | 10.71 | 7.22 | 8.82 | 0.67 | 0.82 | 0.00 | 0.03 | 0.03 |
| Gm26899 | lincRNA | 117.34 | 78.62 | 66.75 | 0.67 | 0.57 | 0.05 | 0.03 | 0.31 |
| 2010320M18Rik | lincRNA | 8.60 | 5.64 | 7.20 | 0.66 | 0.84 | 0.01 | 0.15 | 0.04 |
| Gm14290 | lincRNA | 7.81 | 4.97 | 5.09 | 0.64 | 0.65 | 0.03 | 0.06 | 0.88 |
| Gdap10 | lincRNA | 3.75 | 2.37 | 2.00 | 0.63 | 0.53 | 0.05 | 0.03 | 0.34 |
| A430046D13Rik | lincRNA | 5.64 | 3.55 | 3.06 | 0.63 | 0.54 | 0.02 | 0.01 | 0.49 |
| Gm6712 | lincRNA | 4.83 | 2.55 | 4.45 | 0.53 | 0.92 | 0.02 | 0.38 | 0.02 |
| Yam1 | lincRNA | 35.11 | 17.51 | 107.25 | 0.50 | 3.05 | 0.00 | 0.51 | 0.42 |
| RP23-281H4.12 | lincRNA | 180.51 | 89.32 | 88.44 | 0.49 | 0.49 | 0.01 | 0.01 | 0.96 |
| Gm5532 | lincRNA | 40.21 | 19.88 | 23.44 | 0.49 | 0.58 | 0.00 | 0.02 | 0.43 |
| AW112010 | lincRNA | 40.89 | 19.48 | 24.24 | 0.48 | 0.59 | 0.00 | 0.00 | 0.20 |

Supplementary Table 3: The proteins potentially interacts with GRP94 in cardiomyocytes under hypoxia treatment.

| Protein_ID | GeneName | log2fc | Regulation | HYP-GRP94 | HYP-IgG |
|------------|----------|-------------|------------|------------|-------------|
| P07356 | Anxa2 | 5.436189495 | up | 9.74128123 | 4.305091738 |
| A0A1B0GSX0 | Ldha | 5.331487538 | up | 9.63657928 | 4.305091738 |
| P68033 | Actc1 | 4.992360727 | up | 9.29745246 | 4.305091738 |
| E9Q8K5 | Ttn | 4.929759929 | up | 9.23485167 | 4.305091738 |
| A0A1W2P6F6 | Myl6 | 4.922165998 | up | 9.22725774 | 4.305091738 |
| A0A1B0GQU8 | Rpl18 | 4.811368491 | up | 9.11646023 | 4.305091738 |
| P08249 | Mdh2 | 4.771863326 | up | 9.07695506 | 4.305091738 |
| P63028 | Tpt1 | 4.747389906 | up | 9.05248164 | 4.305091738 |
| P11276 | Fn1 | 4.662475835 | up | 8.96756757 | 4.305091738 |
| Q91YL2 | Rnf126 | 4.637627737 | up | 8.94271948 | 4.305091738 |
| A0A1B0GS70 | Pσμα1 | 4.615023121 | up | 8.92011486 | 4.305091738 |
| F8WIV2 | Serpib6a | 4.587915421 | up | 8.89300716 | 4.305091738 |
| E9PZF5 | Anp32e | 4.560385834 | up | 8.86547757 | 4.305091738 |
| Q6ZWQ9 | Myl12a | 4.50265482 | up | 8.80774656 | 4.305091738 |
| P40124 | Cap1 | 4.480871907 | up | 8.78596365 | 4.305091738 |
| Q6ZQ38 | Cand1 | 4.446803336 | up | 8.75189507 | 4.305091738 |
| Q9R0P3 | Esd | 4.445703302 | up | 8.75079504 | 4.305091738 |
| B1ARA3 | Rpl26 | 4.399292415 | up | 8.70438415 | 4.305091738 |
| F6ZFU0 | Eef1d | 4.383388285 | up | 8.68848002 | 4.305091738 |
| P63158 | Hmgb1 | 4.363272231 | up | 8.66836397 | 4.305091738 |
| D3Z1S8 | Rps5 | 4.352111215 | up | 8.65720295 | 4.305091738 |
| A0A0R4J0Z1 | Pdia4 | 4.339774163 | up | 8.6448659 | 4.305091738 |
| P08228 | Sod1 | 4.316476221 | up | 8.62156796 | 4.305091738 |
| P47738 | Aldh2 | 4.279694908 | up | 8.58478665 | 4.305091738 |
| Q61171 | Prdx2 | 4.238221949 | up | 8.54331369 | 4.305091738 |
| P80317 | Cct6a | 4.222725686 | up | 8.52781742 | 4.305091738 |
| P61205 | Arf3 | 4.212936355 | up | 8.51802809 | 4.305091738 |
| P08207 | S100a10 | 4.200380859 | up | 8.5054726 | 4.305091738 |
| P24472 | Gsta4 | 4.16561957 | up | 8.47071131 | 4.305091738 |
| Q93092 | Taldo1 | 4.147645236 | up | 8.45273697 | 4.305091738 |
| Q99K85 | Psat1 | 4.143443361 | up | 8.4485351 | 4.305091738 |
| P10639 | Txn | 4.137247746 | up | 8.44233948 | 4.305091738 |
| Q8K310 | Matr3 | 4.133595344 | up | 8.43868708 | 4.305091738 |
| P97429 | Anxa4 | 4.129184537 | up | 8.43427628 | 4.305091738 |
| A0A1W2P8C6 | Cd63 | 4.122567091 | up | 8.42765883 | 4.305091738 |
| E9Q905 | Ctnnd1 | 4.11968665 | up | 8.42477839 | 4.305091738 |
| Q8BMD8 | Slc25a24 | 4.113473925 | up | 8.41856566 | 4.305091738 |
| P51410 | Rpl9 | 4.088021194 | up | 8.39311293 | 4.305091738 |
| Q80X68 | Csl | 4.065420076 | up | 8.37051181 | 4.305091738 |
| Q8C483 | Sars | 4.062937154 | up | 8.36802889 | 4.305091738 |

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|---------------|------------|--------------------|-----------|-------------------|--------------------|
| O09131 | Gsto1 | 4.057623752 | up | 8.36271549 | 4.305091738 |
| Q7TMK9 | Syncrip | 4.025631797 | up | 8.33072354 | 4.305091738 |
| Q9CWJ9 | Atic | 4.012488517 | up | 8.31758025 | 4.305091738 |
| Q9CZN7 | Shmt2 | 3.997597222 | up | 8.30268896 | 4.305091738 |
| Q61990 | Pcbp2 | 3.995372603 | up | 8.30046434 | 4.305091738 |
| P50247 | Ahcy | 3.986224333 | up | 8.29131607 | 4.305091738 |
| Q6PCP5 | Mff | 3.977588752 | up | 8.28268049 | 4.305091738 |
| Q9CR16 | Ppid | 3.961938234 | up | 8.26702997 | 4.305091738 |
| K3W4Q8 | Bsg | 3.943551077 | up | 8.24864282 | 4.305091738 |
| Q61598 | Gdi2 | 3.938508686 | up | 8.24360042 | 4.305091738 |
| F6QA74 | Apex1 | 3.913736582 | up | 8.21882832 | 4.305091738 |
| F8WJK8 | St13 | 3.893325738 | up | 8.19841748 | 4.305091738 |
| P23927 | Cryab | 3.892335015 | up | 8.19742675 | 4.305091738 |
| P45376 | Akr1b1 | 3.882427288 | up | 8.18751903 | 4.305091738 |
| Q61553 | Fscn1 | 3.874950199 | up | 8.18004194 | 4.305091738 |
| A2AMW0 | Capzb | 3.866268735 | up | 8.17136047 | 4.305091738 |
| V9GX81 | Mroh6 | 3.843368817 | up | 8.14846055 | 4.305091738 |
| B2RY53 | Gm6133 | 3.829561492 | up | 8.13465323 | 4.305091738 |
| P97315 | Csrp1 | 3.825566599 | up | 8.13065834 | 4.305091738 |
| Q9DBG3 | Ap2b1 | 3.819205301 | up | 8.12429704 | 4.305091738 |
| Q6IFZ6 | Krt77 | 3.81042367 | up | 8.11551541 | 4.305091738 |
| P70349 | Hint1 | 3.802243051 | up | 8.10733479 | 4.305091738 |
| P80316 | Cct5 | 3.794591548 | up | 8.09968329 | 4.305091738 |
| Q61792 | Lasp1 | 3.787584146 | up | 8.09267588 | 4.305091738 |
| P10605 | Ctsb | 3.784783049 | up | 8.08987479 | 4.305091738 |
| B9EKI3 | Tmf1 | 3.775989476 | up | 8.08108121 | 4.305091738 |
| Q9QYB1 | Clic4 | 3.768949105 | up | 8.07404084 | 4.305091738 |
| O35129 | Phb2 | 3.765745817 | up | 8.07083756 | 4.305091738 |
| Q9JJI8 | Rpl38 | 3.761700973 | up | 8.06679271 | 4.305091738 |
| A0A498WFS2 | Ubxn1 | 3.757121132 | up | 8.06221287 | 4.305091738 |
| Q9D0R2 | Tars1 | 3.755288191 | up | 8.06037993 | 4.305091738 |
| Q3V3R1 | Mthfd1l | 3.742138137 | up | 8.04722987 | 4.305091738 |
| P62334 | Psmc6 | 3.74065446 | up | 8.0457462 | 4.305091738 |
| P26443 | Glud1 | 3.737832746 | up | 8.04292448 | 4.305091738 |
| Q3UZG4 | Aimp1 | 3.730994501 | up | 8.03608624 | 4.305091738 |
| P68510 | Ywhah | 3.726293486 | up | 8.03138522 | 4.305091738 |
| Q9R0N0 | Galk1 | 3.715391889 | up | 8.02048363 | 4.305091738 |
| P19157 | Gstp1 | 3.706015202 | up | 8.01110694 | 4.305091738 |
| P35564 | Canx | 3.699229301 | up | 8.00432104 | 4.305091738 |
| A0A338P7H5 | Ahsg | 3.698068617 | up | 8.00316036 | 4.305091738 |
| Q99LC5 | Etfa | 3.68930585 | up | 7.99439759 | 4.305091738 |
| Q8VDM4 | Psmc2 | 3.677461319 | up | 7.98255306 | 4.305091738 |
| Q3TLP8 | Rac1 | 3.67081021 | up | 7.97590195 | 4.305091738 |
| Q91V41 | Rab14 | 3.660687057 | up | 7.9657788 | 4.305091738 |

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|------------|----------|-------------|----|------------|-------------|
| Q9Z2U0 | PsmA7 | 3.63419426 | up | 7.939286 | 4.305091738 |
| Q9D3D9 | Atp5f1d | 3.62582762 | up | 7.93091936 | 4.305091738 |
| Q9D0F9 | Pgm1 | 3.625353744 | up | 7.93044548 | 4.305091738 |
| Q8BKC5 | lpo5 | 3.6005204 | up | 7.90561214 | 4.305091738 |
| P05202 | Got2 | 3.59324538 | up | 7.89833712 | 4.305091738 |
| D3Z2H9 | Tpm3-rs7 | 3.589956565 | up | 7.8950483 | 4.305091738 |
| Q9Z0J0 | Npc2 | 3.572031281 | up | 7.87712302 | 4.305091738 |
| B9EHJ3 | Tjp1 | 3.567004236 | up | 7.87209597 | 4.305091738 |
| Q91VB8 | Hba-a1 | 3.565853694 | up | 7.87094543 | 4.305091738 |
| A0A0G2JGY8 | Rpl34 | 3.560374384 | up | 7.86546612 | 4.305091738 |
| P30416 | Fkbp4 | 3.540267086 | up | 7.84535882 | 4.305091738 |
| P26645 | Marcks | 3.533377424 | up | 7.83846916 | 4.305091738 |
| B7ZNL2 | Nap1l4 | 3.529175206 | up | 7.83426694 | 4.305091738 |
| K3W4L3 | Psap | 3.506472998 | up | 7.81156474 | 4.305091738 |
| A0A384DV79 | Hmga1 | 3.488140243 | up | 7.79323198 | 4.305091738 |
| Q6GT24 | Prdx6 | 3.481423445 | up | 7.78651518 | 4.305091738 |
| P17427 | Ap2a2 | 3.466925094 | up | 7.77201683 | 4.305091738 |
| Q6PFA2 | Clta | 3.464678711 | up | 7.76977045 | 4.305091738 |
| O55135 | Eif6 | 3.462639692 | up | 7.76773143 | 4.305091738 |
| Q9WV55 | Vapa | 3.456330995 | up | 7.76142273 | 4.305091738 |
| P30681 | Hmgb2 | 3.452690788 | up | 7.75778253 | 4.305091738 |
| Q3TPM3 | Cul1 | 3.44528768 | up | 7.75037942 | 4.305091738 |
| Q00612 | G6pdx | 3.433806653 | up | 7.73889839 | 4.305091738 |
| A0A0R4J083 | Acadl | 3.430762894 | up | 7.73585463 | 4.305091738 |
| Q3TW96 | Uap1l1 | 3.398776148 | up | 7.70386789 | 4.305091738 |
| A2A816 | Park7 | 3.365692114 | up | 7.67078385 | 4.305091738 |
| Q05816 | Fabp5 | 3.363254299 | up | 7.66834604 | 4.305091738 |
| G3UVV4 | Hk1 | 3.342141565 | up | 7.6472333 | 4.305091738 |
| Q5NC80 | Nme1 | 3.340612646 | up | 7.64570438 | 4.305091738 |
| Q91YQ5 | Rpn1 | 3.334541029 | up | 7.63963277 | 4.305091738 |
| A0A1W2P7Z3 | Ube2n | 3.317890471 | up | 7.62298221 | 4.305091738 |
| P47226 | Tes | 3.304624824 | up | 7.60971656 | 4.305091738 |
| A2AAW9 | Eif2s3x | 3.296719639 | up | 7.60181138 | 4.305091738 |
| Q9Z2U1 | PsmA5 | 3.286808724 | up | 7.59190046 | 4.305091738 |
| A0A1D5RLV0 | lws1 | 3.284289248 | up | 7.58938099 | 4.305091738 |
| Q9DBG5 | Plin3 | 3.280608907 | up | 7.58570064 | 4.305091738 |
| P99029 | Prdx5 | 3.270450146 | up | 7.57554188 | 4.305091738 |
| A0A286YCD7 | Adk | 3.25790438 | up | 7.56299612 | 4.305091738 |
| P17047 | Lamp2 | 3.248369264 | up | 7.553461 | 4.305091738 |
| A2AEX6 | Fhl1 | 3.235342103 | up | 7.54043384 | 4.305091738 |
| P58774 | Tpm2 | 3.219518965 | up | 7.5246107 | 4.305091738 |
| P47739 | Aldh3a1 | 3.190125876 | up | 7.49521761 | 4.305091738 |
| O88685 | Psmc3 | 3.188530344 | up | 7.49362208 | 4.305091738 |
| Q9CZ13 | Uqcrc1 | 3.18188277 | up | 7.48697451 | 4.305091738 |

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|--------|--------|-------------|----|------------|-------------|
| Q9ERD7 | Tubb3 | 3.17506693 | up | 7.48015867 | 4.305091738 |
| Q9D8B3 | Chmp4b | 3.088436971 | up | 7.39352871 | 4.305091738 |
| O08579 | Emd | 3.082922166 | up | 7.3880139 | 4.305091738 |
| P09055 | Itgb1 | 3.064727143 | up | 7.36981888 | 4.305091738 |
| Q8R5L1 | C1qbp | 3.014044158 | up | 7.3191359 | 4.305091738 |
| P34022 | Ranbp1 | 1.530795502 | up | 9.66544873 | 8.13465323 |
| Q68FD5 | Cltc | 1.50820031 | up | 9.20371017 | 7.695509864 |
| P17742 | Ppia | 1.210432408 | up | 9.43751662 | 8.227084211 |
| Q9D8N0 | Eef1g | 1.205117283 | up | 9.13182836 | 7.926711075 |
| Q61316 | Hspa4 | 1.174333723 | up | 8.69894443 | 7.524610703 |
| P14069 | S100a6 | 1.171042745 | up | 9.32691715 | 8.155874402 |
| P46935 | Nedd4 | 1.117775008 | up | 9.75464308 | 8.63686807 |
| P70168 | Kpnb1 | 1.06905163 | up | 9.10513787 | 8.036086239 |
| Q64727 | Vcl | 1.021969327 | up | 9.06771552 | 8.045746198 |
| P26039 | Tln1 | 1.012865913 | up | 9.07965862 | 8.066792711 |

Supplementary Table 4: The proteins potentially interacts with GRP94 in cardiomyocytes with TN treatment.

| Protein_id | Genename | log2fc | Regulation | TN-GRP94 | TN-IgG |
|---------------|--------------|--------------------|------------|-------------------|--------------------|
| Q6PFC0 | Tbc1d16 | 5.33642663 | up | 9.35246176 | 4.016035134 |
| B1ARA3 | Rpl26 | 4.755611665 | up | 8.7716468 | 4.016035134 |
| P09411 | Pgk1 | 4.754569958 | up | 8.77060509 | 4.016035134 |
| Q8K310 | Matr3 | 4.733013627 | up | 8.74904876 | 4.016035134 |
| F6T4M4 | Srrm1 | 4.716784851 | up | 8.73281999 | 4.016035134 |
| Q6IFZ6 | Krt77 | 4.629394265 | up | 8.6454294 | 4.016035134 |
| B9EKI3 | Tmf1 | 4.517290356 | up | 8.53332549 | 4.016035134 |
| P26645 | Marcks | 4.485012561 | up | 8.5010477 | 4.016035134 |
| Q8BHC4 | Dcakd | 4.466255396 | up | 8.48229053 | 4.016035134 |
| P07356 | Anxa2 | 4.442867108 | up | 8.45890224 | 4.016035134 |
| E9Q8D0 | Dnajc21 | 4.437686785 | up | 8.45372192 | 4.016035134 |
| E9PZF5 | Anp32e | 4.403290262 | up | 8.4193254 | 4.016035134 |
| P63101 | Ywhaz | 4.39309955 | up | 8.40913468 | 4.016035134 |
| Q91YL2 | Rnf126 | 4.377332283 | up | 8.39336742 | 4.016035134 |
| D3Z2H2 | Ctnnd1 | 4.285636001 | up | 8.30167114 | 4.016035134 |
| O89086 | Rbm3 | 4.266118831 | up | 8.28215397 | 4.016035134 |
| P06327 | Gm5629 | 4.233707314 | up | 8.24974245 | 4.016035134 |
| A6ZI44 | Aldoa | 4.230316084 | up | 8.24635122 | 4.016035134 |
| Q7SIG6 | Asap2 | 4.122955728 | up | 8.13899086 | 4.016035134 |
| Q3TML0 | Pdia6 | 4.066390077 | up | 8.08242521 | 4.016035134 |
| Q6PCP5 | Mff | 4.028734267 | up | 8.0447694 | 4.016035134 |
| P62259 | Ywhae | 3.986889389 | up | 8.00292452 | 4.016035134 |
| Q9D1E6 | Tbcb | 3.904700852 | up | 7.92073599 | 4.016035134 |
| P28033 | Cebpb | 3.891917832 | up | 7.90795297 | 4.016035134 |
| Q3UMU9 | Hdgfl2 | 3.879585165 | up | 7.8956203 | 4.016035134 |
| P04104 | Krt1 | 3.82970624 | up | 7.84574137 | 4.016035134 |
| Q5NCC2 | Trim41 | 3.814175288 | up | 7.83021042 | 4.016035134 |
| Q8VE37 | Rcc1 | 3.807877273 | up | 7.82391241 | 4.016035134 |
| Q64523 | H2ac20 | 3.774588941 | up | 7.79062408 | 4.016035134 |
| Q9D0E1 | Hnrnpm | 3.767483985 | up | 7.78351912 | 4.016035134 |
| P63323 | Rps12 | 3.759163421 | up | 7.77519855 | 4.016035134 |
| Q61696 | Hspa1a | 3.750734703 | up | 7.76676984 | 4.016035134 |
| A0A0G2JF72 | Csde1 | 3.585864744 | up | 7.60189988 | 4.016035134 |
| Q8BX02 | Kank2 | 3.570638305 | up | 7.58667344 | 4.016035134 |
| Q9D024 | Ccdc47 | 3.554854187 | up | 7.57088932 | 4.016035134 |
| Q1HFZ0 | Nsun2 | 3.53309656 | up | 7.54913169 | 4.016035134 |
| A2AWT7 | Ubtf | 3.455826932 | up | 7.47186207 | 4.016035134 |
| Q6IFX2 | Krt42 | 3.447533533 | up | 7.46356867 | 4.016035134 |
| O70503 | Hsd17b12 | 3.432714332 | up | 7.44874947 | 4.016035134 |
| Q9Z110 | Aldh18a1 | 3.402928393 | up | 7.41896353 | 4.016035134 |

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|------------|----------|-------------|----|------------|-------------|
| A0A1B0GR19 | Rcn3 | 3.358651263 | up | 7.3746864 | 4.016035134 |
| Q6PFA2 | Clta | 3.356891914 | up | 7.37292705 | 4.016035134 |
| P63271 | Supt4h1a | 3.355124565 | up | 7.3711597 | 4.016035134 |
| E9QA50 | Ifrd1 | 3.336754703 | up | 7.35278984 | 4.016035134 |
| A0A0A0MQM2 | Plch1 | 3.309517631 | up | 7.32555277 | 4.016035134 |
| Q91VB8 | Hba-a1 | 3.306809081 | up | 7.32284422 | 4.016035134 |
| Q6ZQ38 | Cand1 | 3.293128981 | up | 7.30916412 | 4.016035134 |
| P80316 | Cct5 | 3.287243319 | up | 7.30327845 | 4.016035134 |
| A0A0G2JG10 | Dhx15 | 3.282187728 | up | 7.29822286 | 4.016035134 |
| A0A140LI98 | Uqcrc2 | 3.275455337 | up | 7.29149047 | 4.016035134 |
| D3YZJ1 | Sqstm1 | 3.258015937 | up | 7.27405107 | 4.016035134 |
| A0A2R8W6S4 | Pacsin2 | 3.228761544 | up | 7.24479668 | 4.016035134 |
| Q9D8L3 | Ssr4 | 3.219148379 | up | 7.23518351 | 4.016035134 |
| Q9R0I7 | Ylpm1 | 3.16206824 | up | 7.17810337 | 4.016035134 |
| F6ZQL0 | Mtdh | 3.117500771 | up | 7.13353591 | 4.016035134 |
| Q00623 | Apoa1 | 3.096860077 | up | 7.11289521 | 4.016035134 |
| A0A087WQ14 | Actr3 | 3.096277995 | up | 7.11231313 | 4.016035134 |
| Q6P5B5 | Fxr2 | 3.089008427 | up | 7.10504356 | 4.016035134 |
| A0A0G2JDU0 | Igkv8-34 | 3.087304987 | up | 7.10334012 | 4.016035134 |
| Q9D823 | Rpl37 | 2.973376371 | up | 6.98941151 | 4.016035134 |
| P61620 | Sec61a1 | 2.915647099 | up | 6.93168223 | 4.016035134 |
| Q61048 | Wbp4 | 2.892928138 | up | 6.90896327 | 4.016035134 |
| A0A0R4J0Z1 | Pdia4 | 2.208682463 | up | 9.50017294 | 7.291490472 |
| P34022 | Ranbp1 | 2.149226649 | up | 9.46042562 | 7.311198973 |
| O08796 | Eef2k | 2.080534191 | up | 9.15431662 | 7.073782425 |
| P46935 | Nedd4 | 1.53452678 | up | 9.81668075 | 8.282153966 |
| Q68FD5 | Cltc | 1.479129255 | up | 8.74338243 | 7.264253177 |
| P68372 | Tubb4b | 1.404287877 | up | 10.0084828 | 8.60419496 |
| Q8C2Q7 | Hnrnp1 | 1.133161008 | up | 9.05289305 | 7.919732044 |
| G3X956 | Supt16 | 1.046948886 | up | 8.89161797 | 7.844669084 |
| Q52KR3 | Prune2 | 1.015647044 | up | 9.12917088 | 8.113523835 |