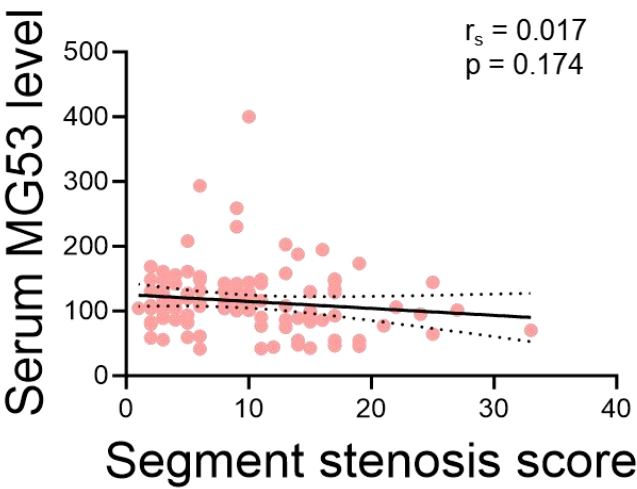
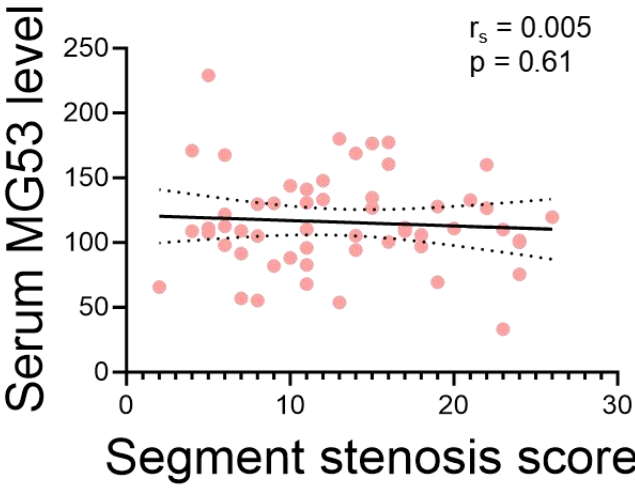


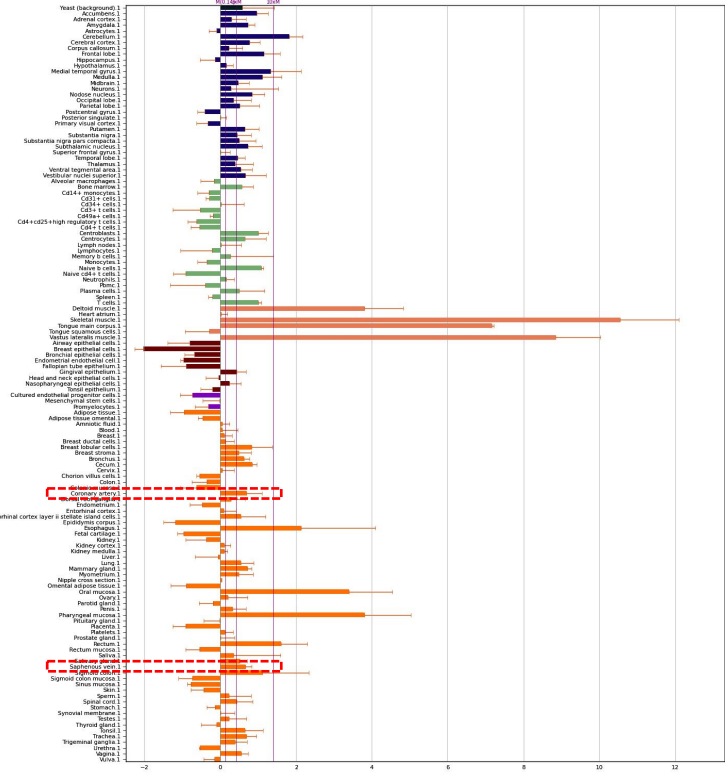
A



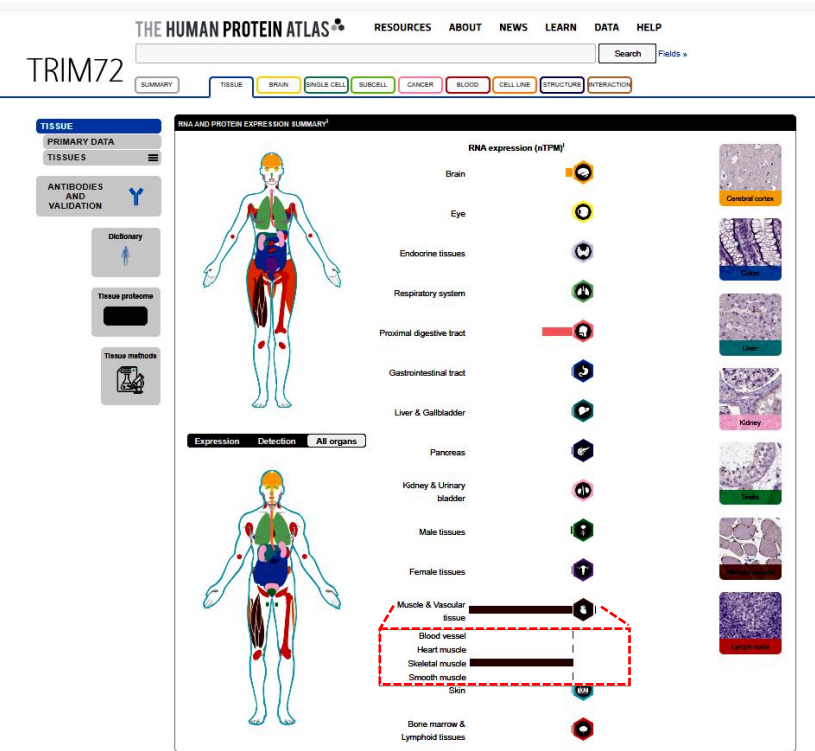
B



C



D



E

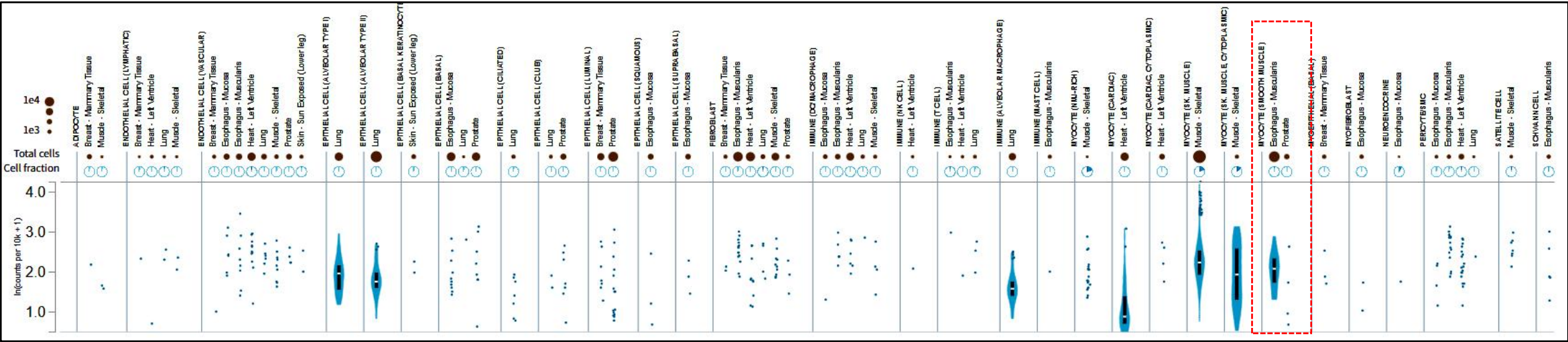


Figure S1. A and B, Correlation of serum MG53 levels with segment stenosis score in CAD patients with **(A, n=55)** or without **(B, n=107)** myocardial injury. **C-E**, Publicly available human gene and protein expression databases, including Biological Gene Portal System (BioGPS, **C**), Human Protein Atlas (HPA, **D**), and Genotype-Tissue Expression (GTEx, **E**) project, were used to delineate tissue-specific and cellular distribution of MG53. Data are presented as mean±SEM. S1A and S1B, Spearman's correlation.

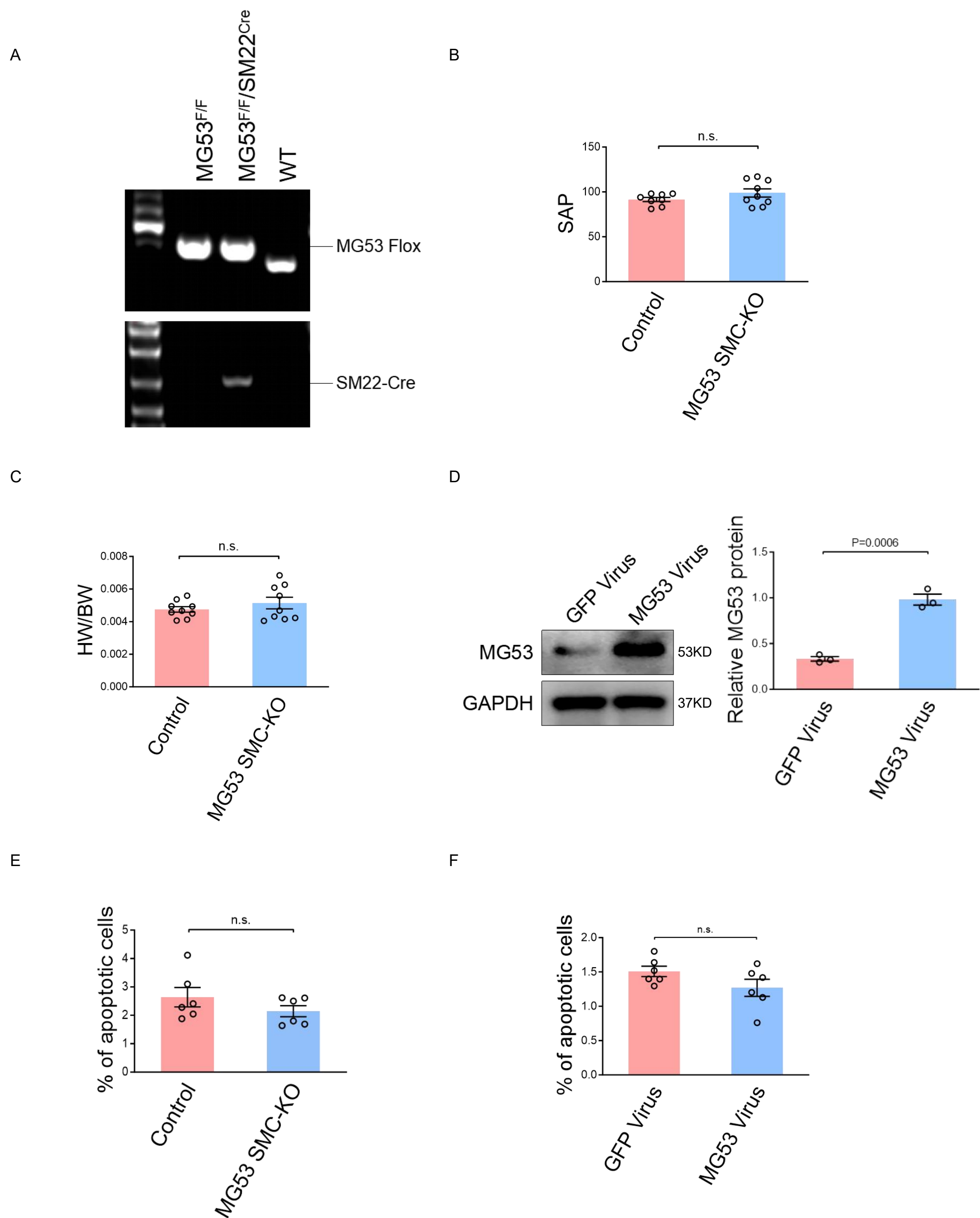
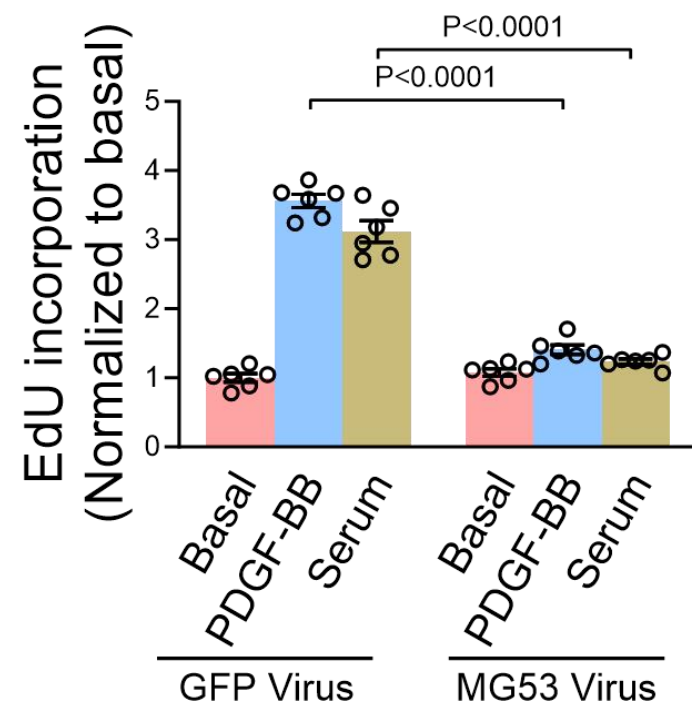
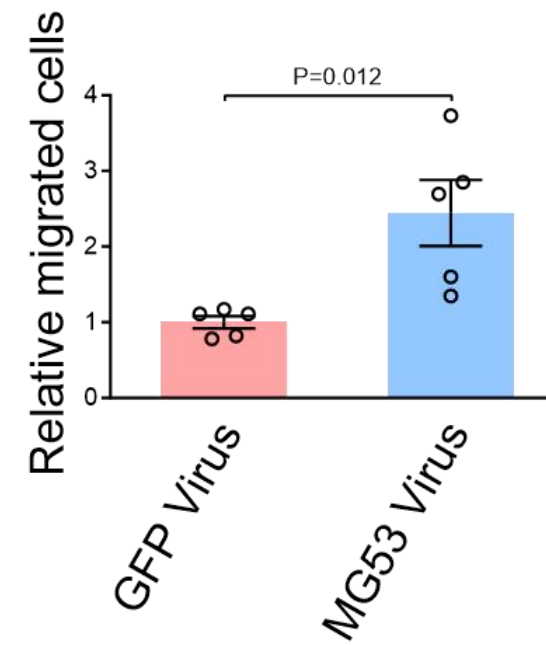


Figure S2. **A**, Genotyping of SMC-specific MG53-KO mice by PCR of genomic DNA. **B** and **C**, Systemic arterial pressure (SAP, **B**) and heart weight to body weight ratio (HW/BW, **C**) of control and SMC-specific MG53-KO mice. n=9. **D**, MG53 protein level in human aortic SMCs transfected with GFP or MG53 virus. n=3. **E** and **F**, Cell apoptosis was analyzed by flow cytometry using annexin V and 7AAD staining in primary vascular SMCs isolated from control and MG53 SMC-KO mice (**E**), or transfected with GFP or MG53 virus (**F**). n=6. Data are presented as mean±SEM. S2B - S2F, Kruskal-Wallis test.

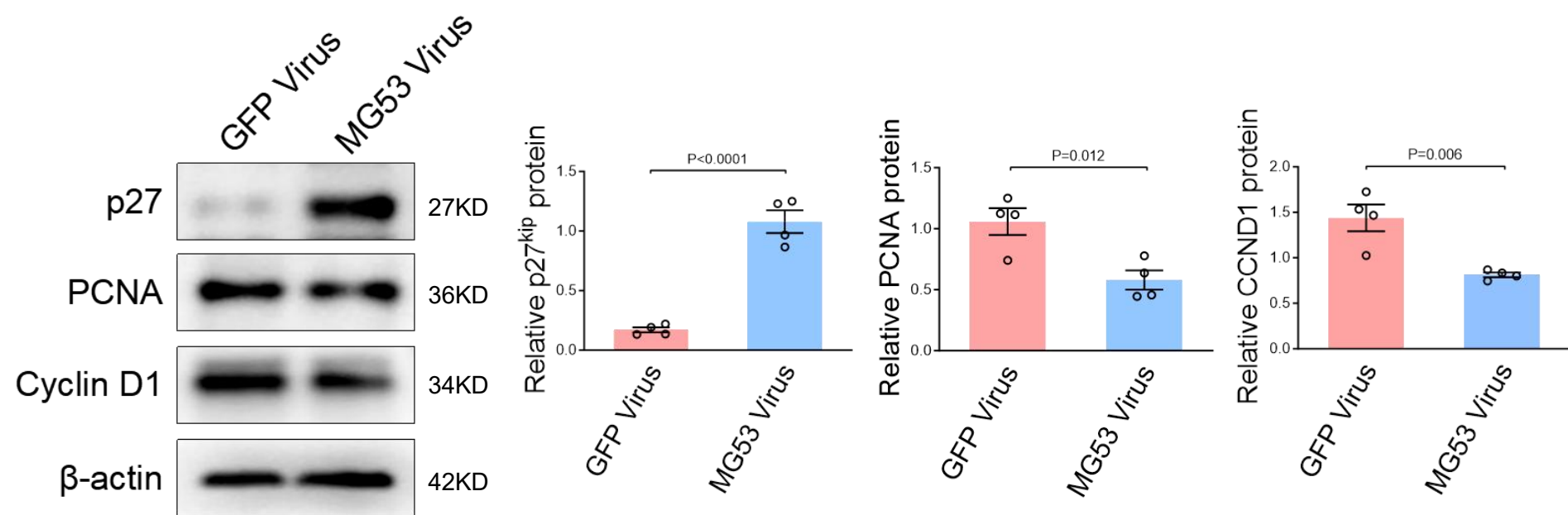
A



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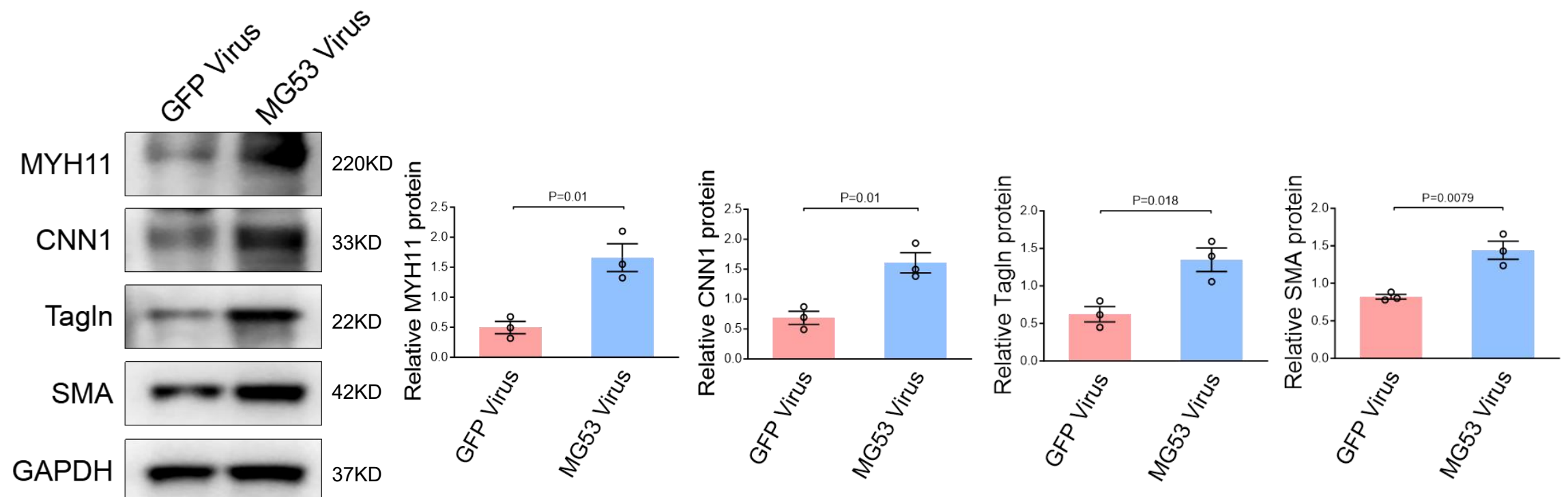


Figure S3. **A**, Human aortic SMCs were transfected with GFP or MG53 virus, and cell proliferation in response to PDGF-BB and serum stimulation was quantified by 5-ethynyl-2'-deoxyuridine (EdU) incorporation. n=6. **B**, Cell migration of human SMCs transfected with GFP or MG53 virus was assessed by transwell assay. n=5. **C**, Protein levels of p27^{Kip1}, PCNA, and Cyclin D1 in human SMCs transfected with GFP or MG53 virus, assessed by Western blot analysis. n=4. **D**, Effects of MG53 overexpression on protein levels of MYH11, CNN1, Tagln, and SMA in SMCs, assessed by Western blot analysis. n=3. Data are presented as mean $\pm$ SEM. S3B - S3D, Kruskal-Wallis test.

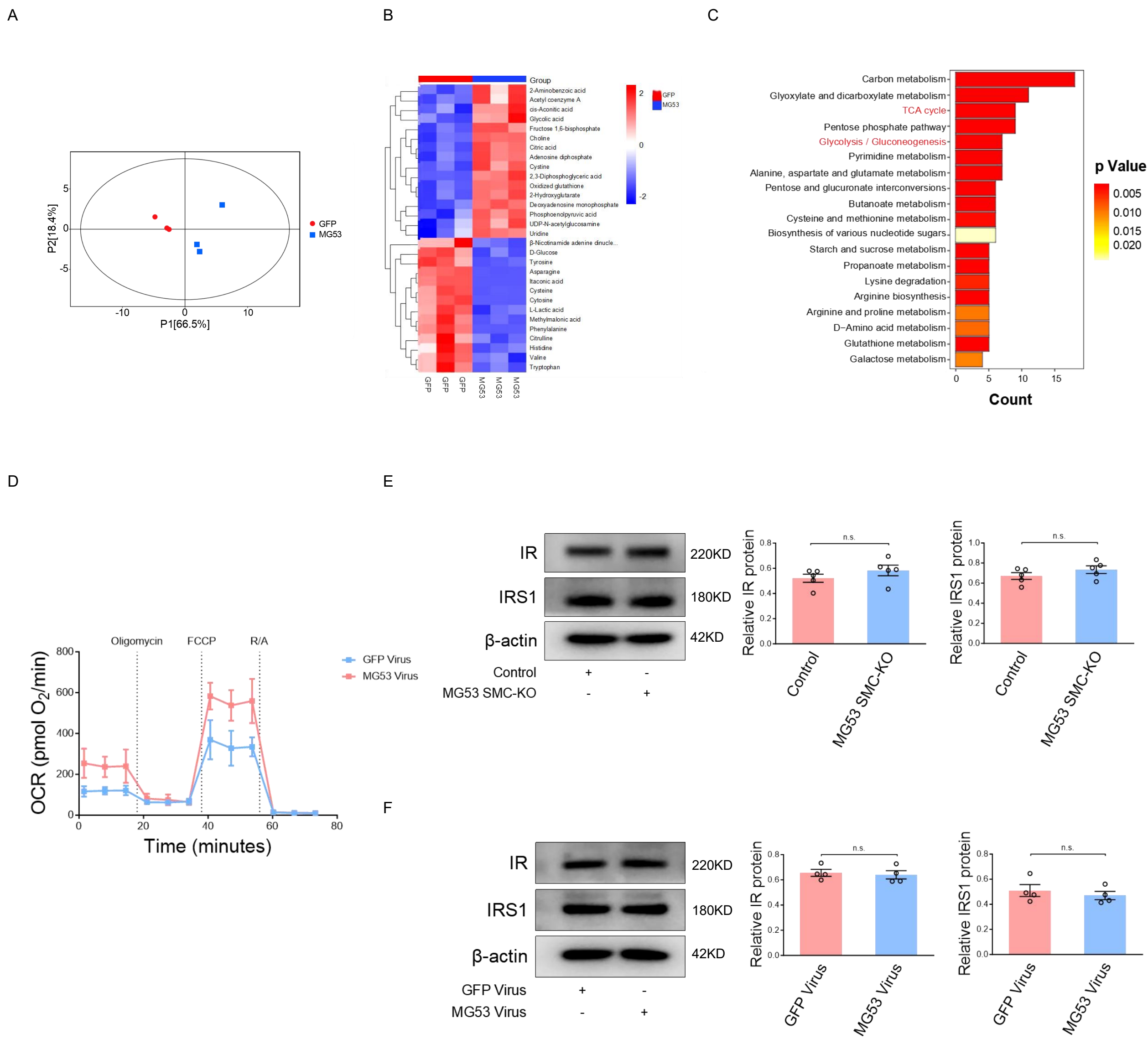


Figure S4. **A**, Partial least squares discriminant analysis of the indicated samples. The dots represent SMCs transfected with GFP (red) or MG53 virus (blue). **B**, Heat map illustrating the top 30 differentially expressed metabolites. **C**, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed using differential metabolites revealed by metabolomics analysis. Glucose metabolites are in red. **D**, Traces of oxygen consumption rate of SMCs transfected with GFP or MG53 virus measured using the Seahorse XF96 flux analyzer, with sequential injections at time points indicated. $n=4$. **E** and **F**, Effects of MG53 depletion (**E**, $n=5$) or overexpression (**F**, $n=4$) on protein levels of insulin receptor (IR) and insulin receptor substrate 1 (IRS1), assessed by Western blot analysis. Data are presented as mean $\pm$ SEM. S4E and S4F, Kruskal-Wallis test.

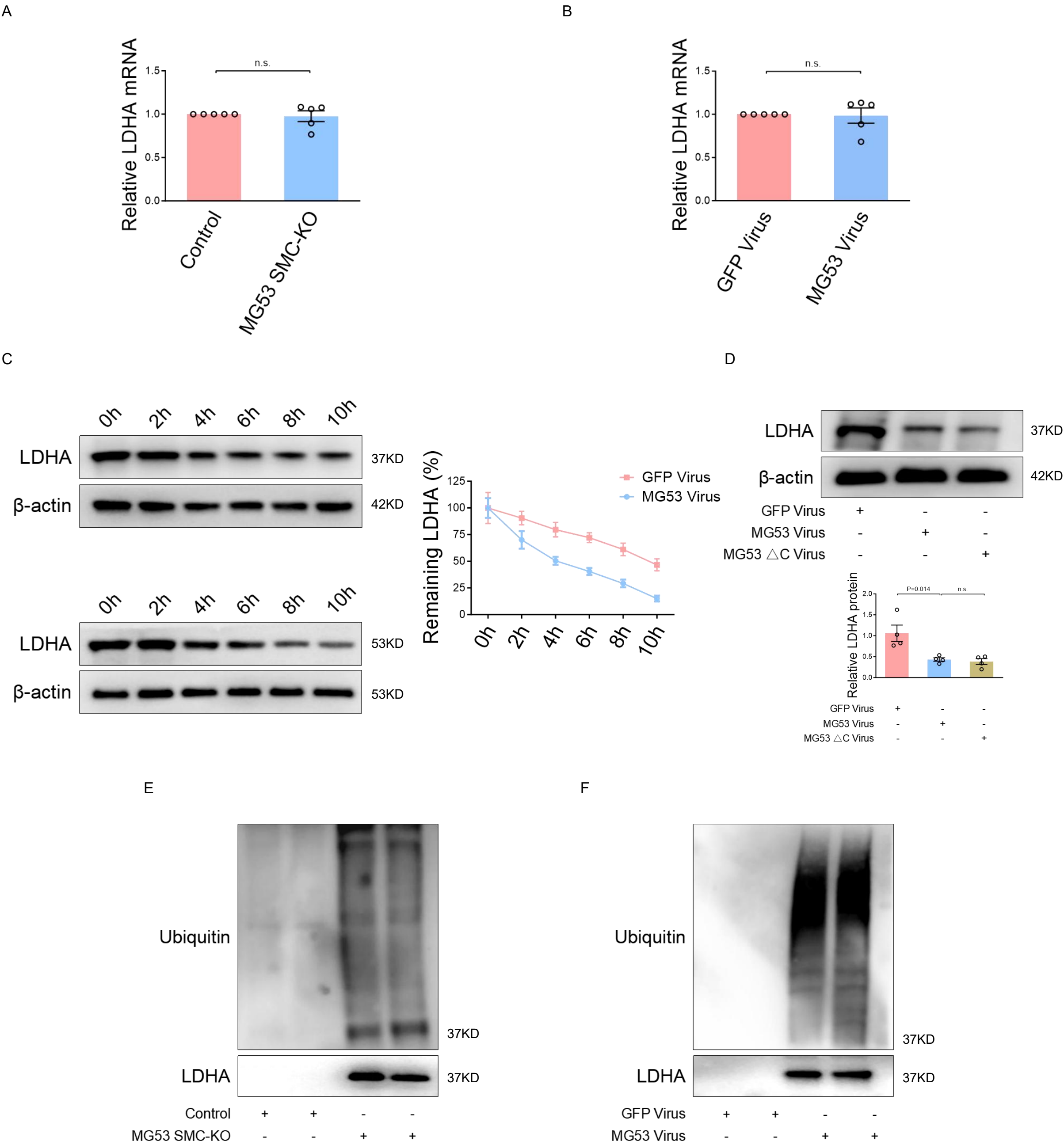


Figure S5. **A** and **B**, Effects of MG53 depletion (**A**) or overexpression (**B**) on LDHA mRNA level in primary SMCs, assessed by RT-PCR. $n=3$. **C**, SMCs transfected with GFP control or MG53-overexpression virus were treated with 10 μ g/ml chloroquine, and LDHA protein levels were determined. $n=3$. **D**, SMCs were transfected with with GFP, MG53 overexpressing, or MG53 Δ C virus. Protein levels of LDHA were assessed by Western blot analysis. $n=4$. **E**, The lysates from SMCs isolated from control and MG53 SMC-KO mice were incubated with IgG or anti-LDHA antibody. The immunoprecipitates were analyzed by immunoblotting with an anti-ubiquitin antibody. **F**, The effect of MG53 overexpression on LDHA ubiquitination was assessed by coimmunoprecipitation. Data are presented as mean $\pm$ SEM. S5A and S5B, Kruskal-Wallis test; S5D, 2-way ANOVA.

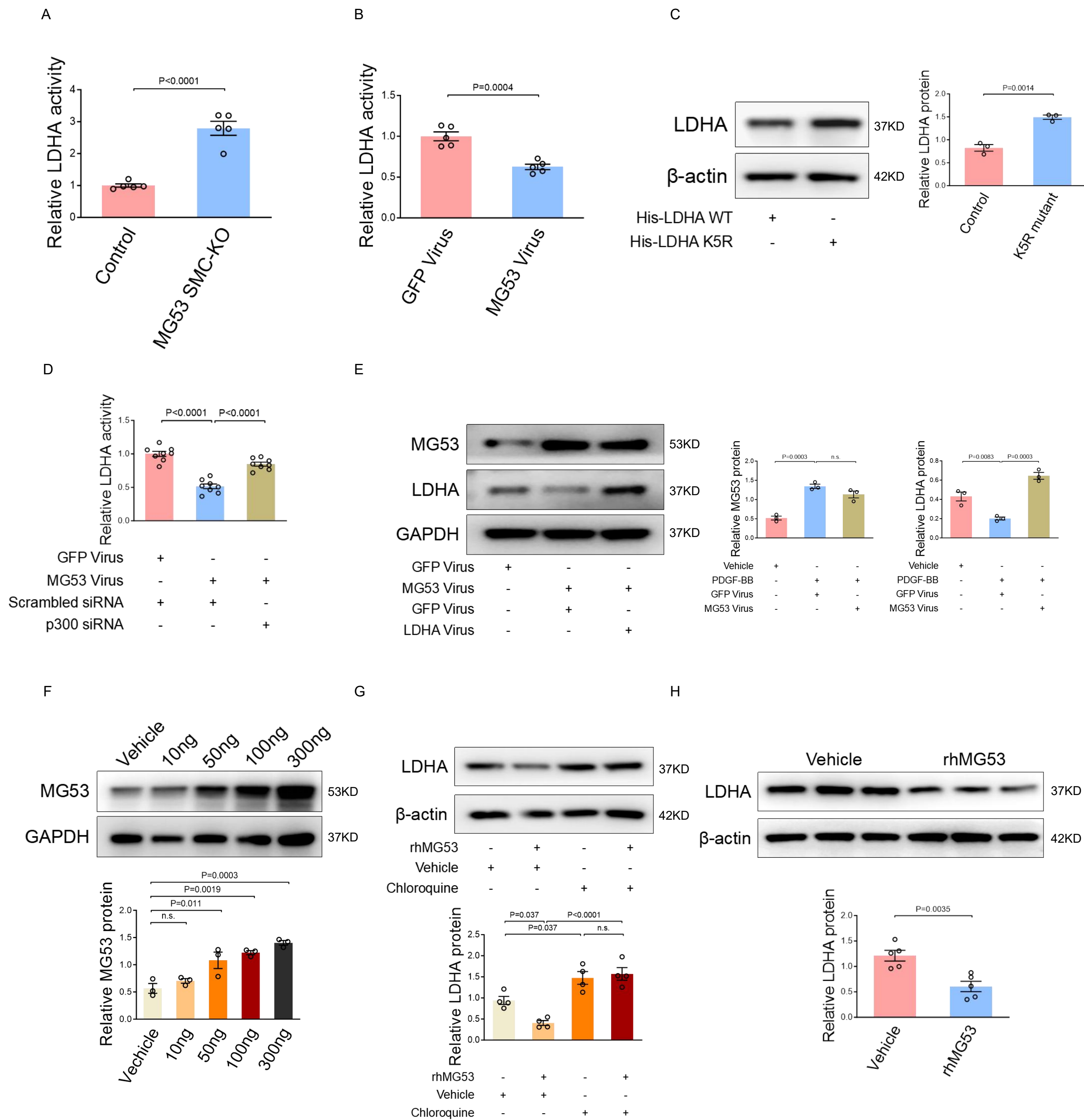


Figure S6. **A** and **B**, Effects of MG53 depletion (**A**) and overexpression (**B**) on LDHA activity in SMCs, assessed using LDH activity assay kit. $n=5$. **C**, Western blot showing LDHA protein levels in SMCs transfected with wild-type or K5R mutant LDHA vector. $n=3$. **D**, Effects of MG53 overexpression on LDHA activity in the presence or absence of P300-specific siRNA, assessed using LDH activity assay kit. $n=8$. **E**, Representative Western blot of MG53 and LDHA protein in SMCs transfected with GFP or MG53 virus plus GFP or LDHA virus. $n=3$. **F**, MG53 protein levels in SMCs treated with different concentrations of rhMG53, assessed by Western blot analysis. $n=3$. **G**, SMCs were incubated with or without rhMG53 and treated with chloroquine (10 μ g/ml). LDHA protein levels were measured by Western blot analysis. $n=4$. **H**, Protein levels of LDHA in injured rat carotid arteries treated with or without rhMG53 were assessed by Western blot analysis. $n=5$. Data are presented as mean $\pm$ SEM. S6A - S6C, Kruskal-Wallis test; S6D, S6E, and S6G, 2-way ANOVA; S6F, 1-way ANOVA; S6H, Kruskal-Wallis test.