Supplementary Table 1

Echocardiography analysis of Prmt5 knockout mice in periostin-positive cells after TAC surgery

	Sham		TAC	
	Prmt5$^{fl/fl}$	*Postn*^{MCM}; *Prmt5*$^{fl/fl}$	*Prmt5*$^{fl/fl}$	*Postn*^{MCM}; *Prmt5*$^{fl/fl}$
LVIDd, mm	2.7 ± 0.4	2.5 ± 0.2	2.8 ± 0.4*	2.2 ± 0.2$^{\#\#}$
LVPWd, mm	0.9 ± 0.1	0.8 ± 0.1	1.4 ± 0.2***	1.0 ± 0.1$^{\#}$
LVIDs, mm	1.2 ± 0.3	1.1 ± 0.1	1.9 ± 0.4***	1.1 ± 0.3$^{\#\#\#}$
LVPWs, mm	1.2 ± 0.1	1.1 ± 0.1	1.2 ± 0.3	1.1 ± 0.1
FS, %	56.3 ± 4.7	57.4 ± 4.2	33.6 ± 7.7***	50.9 ± 10.4$^{\#}$

Data show the mean ± SD.

Two-way ANOVA, followed by Tukey's multiple-comparisons test.

Significant differences are indicated as follows:

* p <0.05, *** p < 0.001 vs Sham-operated *Prmt5*$^{fl/fl}$ group

# p < 0.05, ## p < 0.01, ### p < 0.001 vs TAC-operated *Prmt5*$^{fl/fl}$ group

LVIDd; left ventricular internal dimension at diastolic, LVPWd; left ventricular posterior wall thickness at diastolic, LVIDs; left ventricular internal dimension at systolic, LVPWs; left ventricular posterior wall thickness at systolic, FS; fractional shortening

Supplementary Table 2
Echocardiography analysis of Prmt5 knockout mice in col1a2 positive cells after TAC surgery

	Sham		TAC	
	Prmt5$^{fl/fl}$	*Col1a2*^{MCM}; *Prmt5*$^{fl/fl}$	*Prmt5*$^{fl/fl}$	*Col1a2*^{MCM}; *Prmt5*$^{fl/fl}$
LVIDd, mm	2.7 ± 0.3	2.3 ± 0.4	2.7 ± 0.4	2.4 ± 0.6$^{\#\#}$
LVPWd, mm	0.8 ± 0.1	0.9 ± 0.1	1.2 ± 0.2***	1.1 ± 0.1$^{\#}$
LVIDs, mm	1.1 ± 0.2	1.0 ± 0.2	1.7 ± 0.3***	1.3 ± 0.5$^{\#\#\#}$
LVPWs, mm	1.1 ± 0.1	1.2 ± 0.1	1.4 ± 0.2	1.3 ± 0.3
FS, %	59.1 ± 5.2	55.2 ± 4.4	36.2 ± 7.2***	48.9 ± 13.0$^{\#}$

Data show the mean ± SD.
Two-way ANOVA, followed by Tukey's multiple-comparisons test.
Significant differences are indicated as follows:
*** $p < 0.001$ vs Sham-operated *Prmt5*$^{fl/fl}$ group
# $p < 0.05$, ## $p < 0.01$, ### $p < 0.001$ vs TAC-operated *Prmt5*$^{fl/fl}$ group

LVIDd; left ventricular internal dimension at diastolic, LVPWd; left ventricular posterior wall thickness at diastolic, LVIDs; left ventricular internal dimension at systolic, LVPWs; left ventricular posterior wall thickness at systolic, FS; fractional shortening

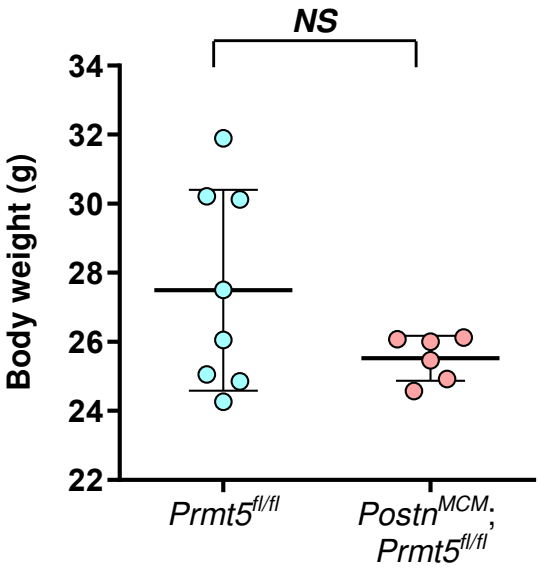
A

【***Postn*^{MCM}; *Prmt5*$^{fl/fl}$】**

sex	No. of live mice	Genotype of live mice	
		Prmt5$^{fl/fl}$	*Postn*^{MCM}; *Prmt5*$^{fl/fl}$
♂	123	76	47
		33.6%	20.8%
♀	103	51	52
		22.6%	23.0%

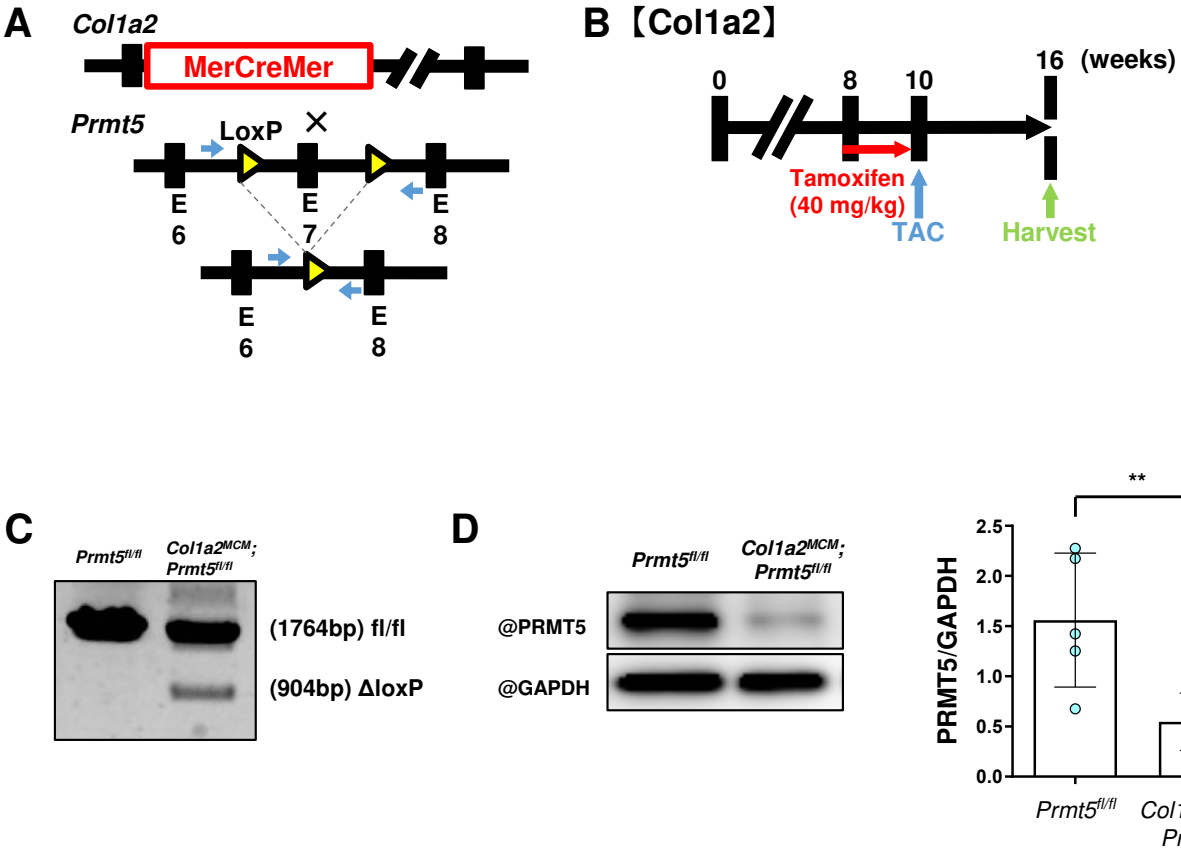
sex	No. of live mice	Genotype of live mice	
		Prmt5$^{fl/fl}$	*Postn*^{MCM}; *Prmt5*$^{fl/fl}$
♂♀	226	127	99
		56.2%	43.8%

B



Supplementary Figure 1

Postn^{MCM}*; Prmt5*$^{fl/fl}$ mice were born in an expected Mendelian ratio (A). The body weight of these mice was not significantly different from that of *Prmt5*$^{fl/fl}$ mice (B). Values are presented as mean ± SD (n = 6-8 mice/group). NS: no significant difference.



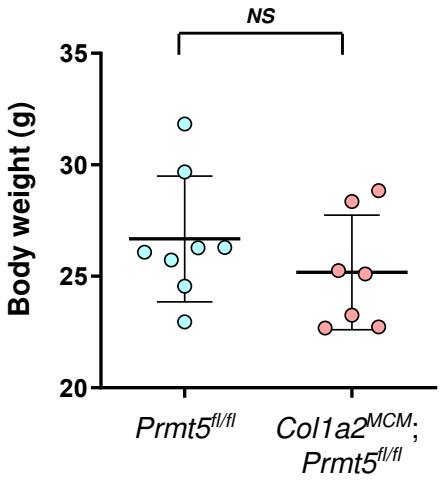
E

【*Col1a2*^{MCM}; *Prmt5*$^{fl/fl}$】

sex	No. of live mice	Genotype of live mice	
		Prmt5$^{fl/fl}$	*Col1a2*^{MCM}; *Prmt5*$^{fl/fl}$
♂	164	77	87
		23.2%	26.2%
♀	168	95	73
		28.6%	22.0%

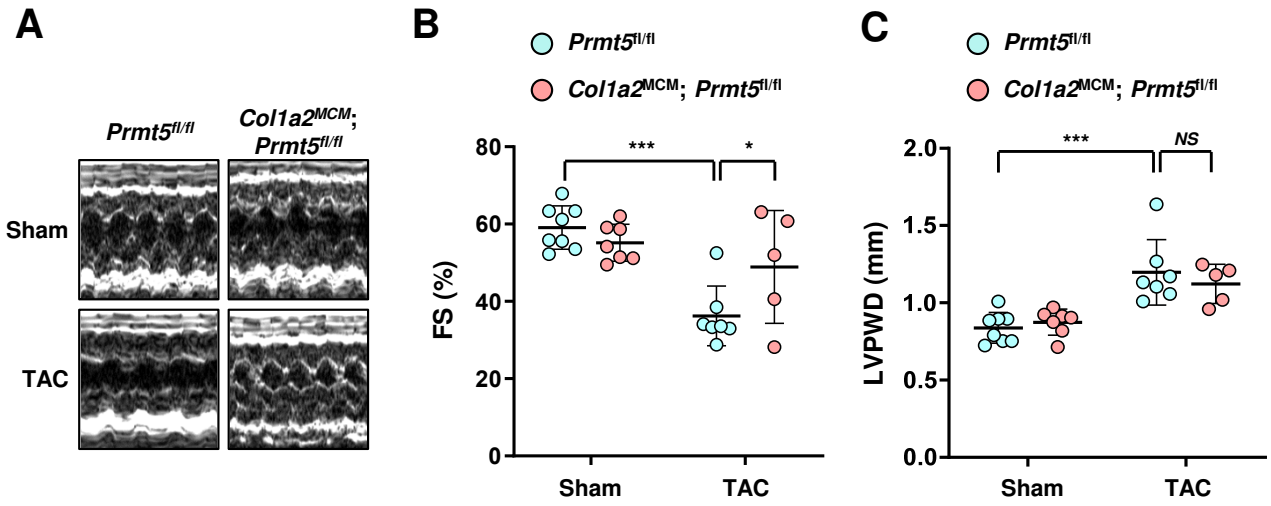
sex	No. of live mice	Genotype of live mice	
		Prmt5$^{fl/fl}$	*Col1a2*^{MCM}; *Prmt5*$^{fl/fl}$
♂♀	332	172	160
		51.8%	48.2%

F



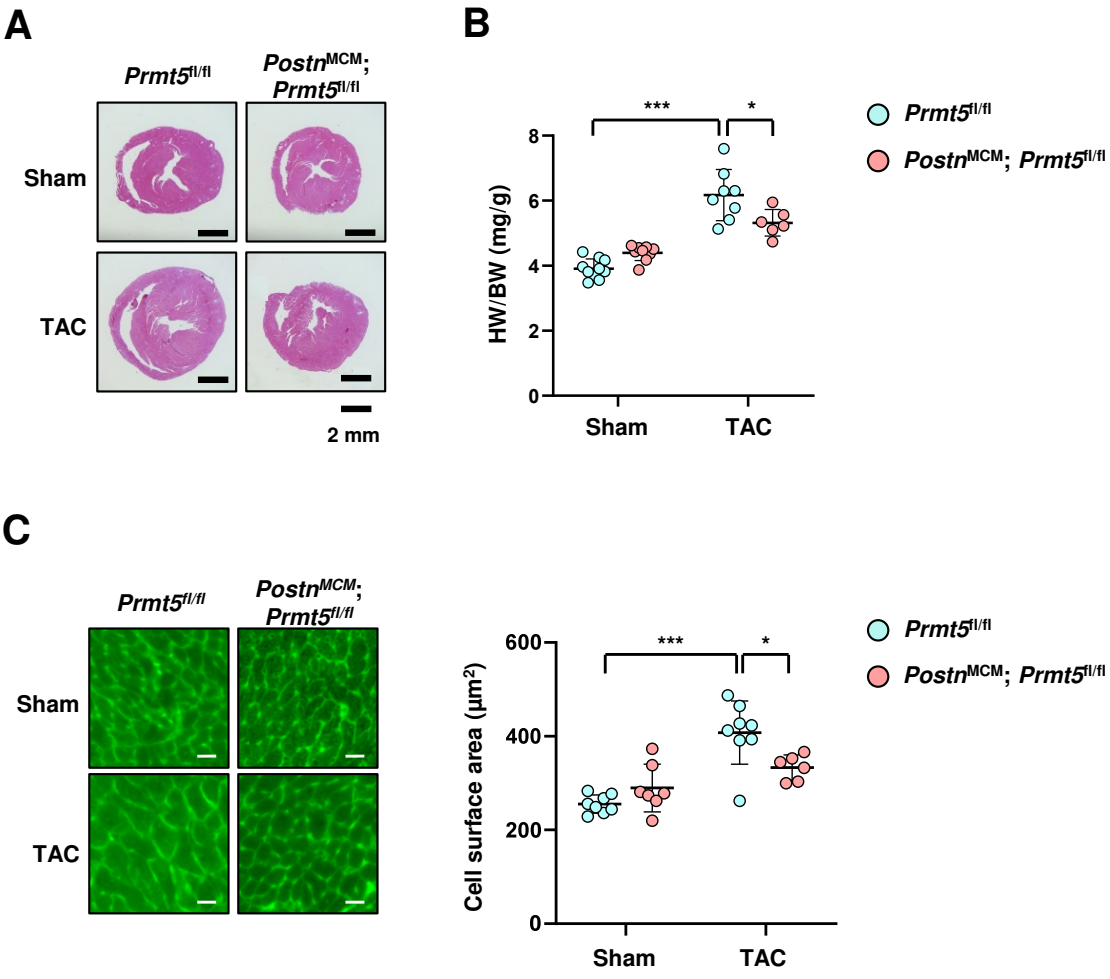
Supplementary Figure 2

The knockout of *Prmt5* in the fibroblasts of *Col1a2*^{MCM}*; Prmt5*$^{fl/fl}$ mice was confirmed by western blot analysis. Fibroblasts from tamoxifen-treated mice were cultured, and their genome DNA and protein expression was determined (A-D). Values are presented as mean ± SD (n = 5-7 mice/group). *Prmt5* knockout in Col1a2-positive fibroblasts did not cause significant changes in lethality or growth in the mice. The mice were born in an expected Mendelian ratio (E). The body weight of these mice was not significantly different from that of *Prmt5*$^{fl/fl}$ mice (F). Values are presented as mean ± SD (n = 7-8 mice/group). ** $p < 0.01$. NS: no significant difference.



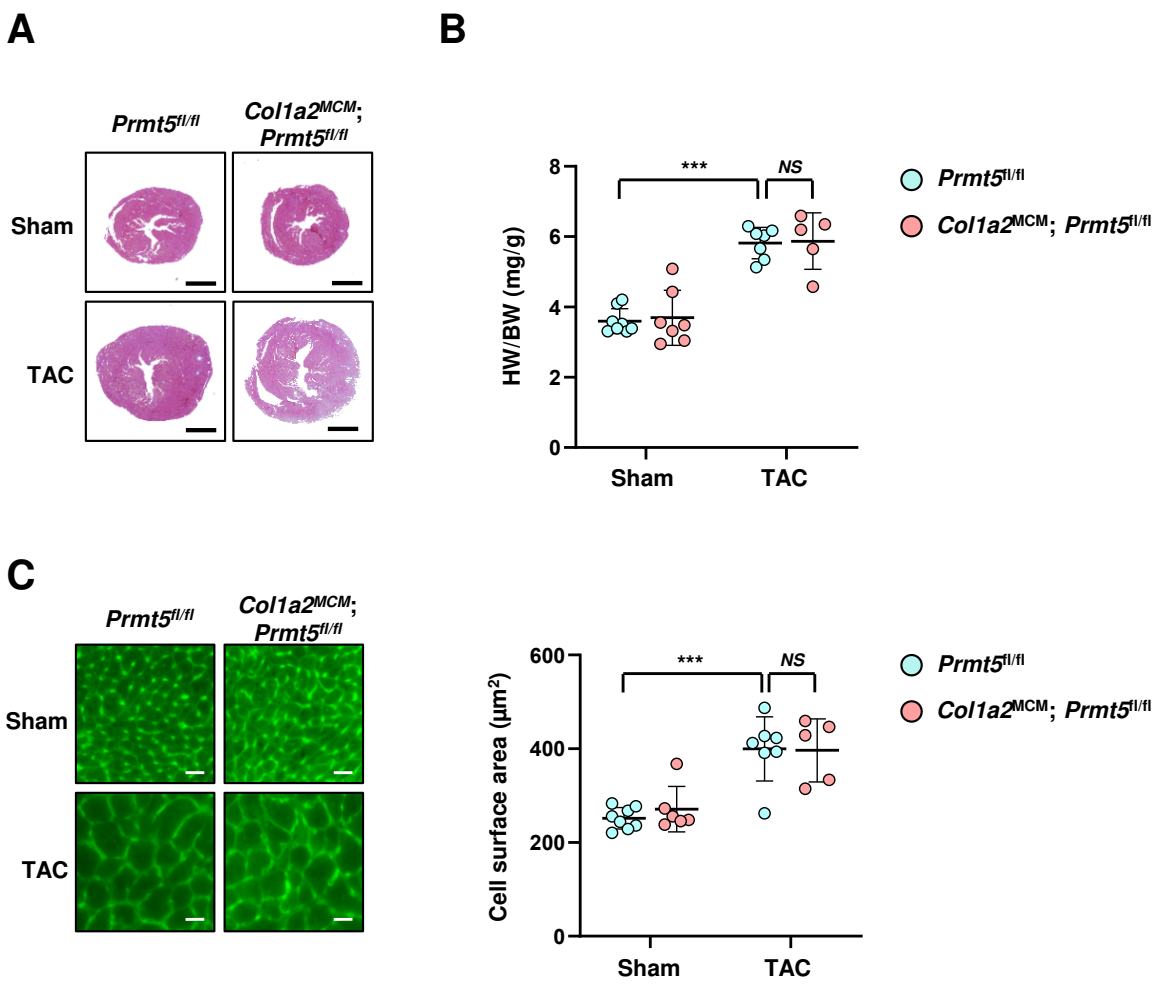
Supplementary Figure 3

Prmt5 knockout in fibroblasts suppresses cardiac dysfunction induced by pressure overload. *Prmt5* deficiency in fibroblast lineages attenuates pressure overload-induced cardiac dysfunction. Echocardiography analysis was performed on *Col1a2*^{MCM}*; Prmt5*$^{fl/fl}$ and *Prmt5*$^{fl/fl}$ mice at 8 weeks after TAC surgery. Fractional shorting was calculated. Values are presented as mean ± SD (n = 5-8 mice/group). Two-way ANOVA, followed by Tukey's multiple-comparisons test. * $p < 0.05$, *** $p < 0.001$. NS: no significant difference.



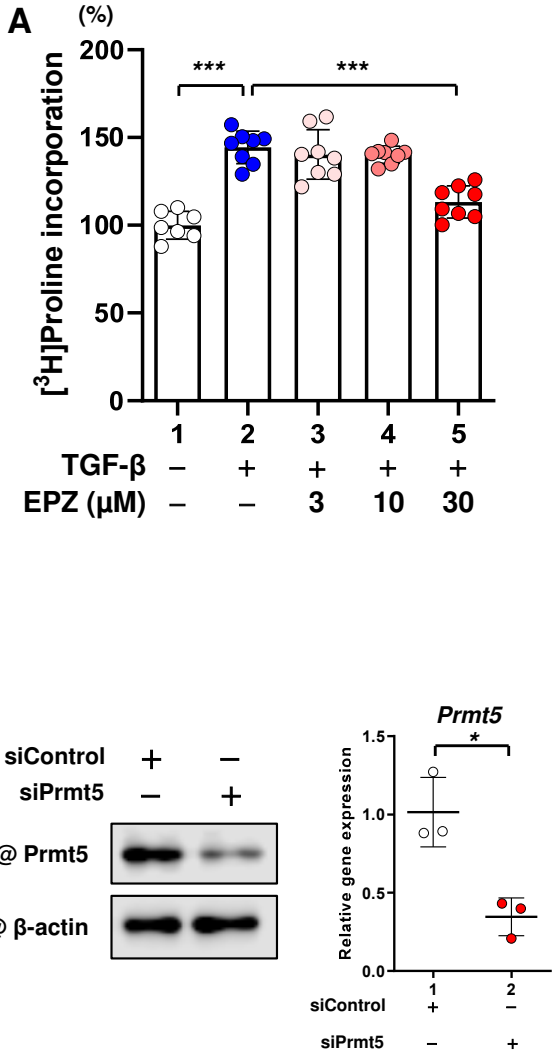
Supplementary Figure 4

Prmt5 knockout in *Postn*-positive fibroblasts suppresses cardiac hypertrophy induced by pressure overload. Representative images of heart tissue are shown. Heart-weight-to-body-weight ratio was calculated 8 weeks after TAC surgery (A). The surface of the cardiomyocytes was stained with FITC-labeled wheat germ agglutinin and their area was determined with ImageJ software (B). Values are presented as mean ± SD (n = 6-8 mice/group). Two-way ANOVA, followed by Tukey's multiple-comparisons test. * $p < 0.05$, *** $p < 0.001$.



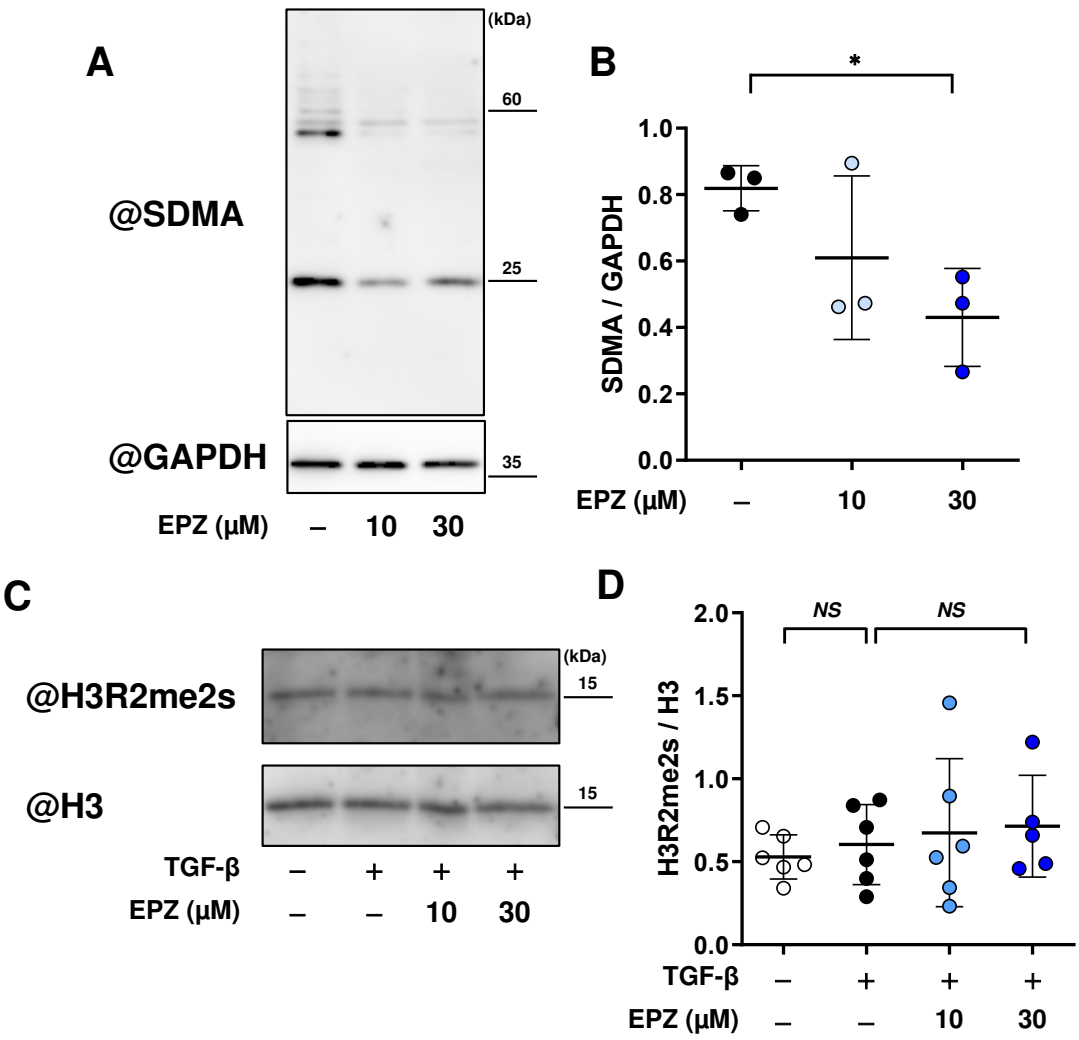
Supplementary Figure 5

Prmt5 knockout in *Col1a2*-positive fibroblasts suppresses cardiac hypertrophy induced by pressure overload. Representative images of heart tissue are shown. Heart-weight-to-body-weight ratio was calculated 8 weeks after TAC surgery (A). The surface of the cardiomyocytes was stained with FITC-labeled wheat germ agglutinin and their area was determined with ImageJ software (B). Values are presented as mean ± SD (n = 5-8 mice/group). Two-way ANOVA, followed by Tukey's multiple-comparisons test. * $p < 0.05$, *** $p < 0.001$.



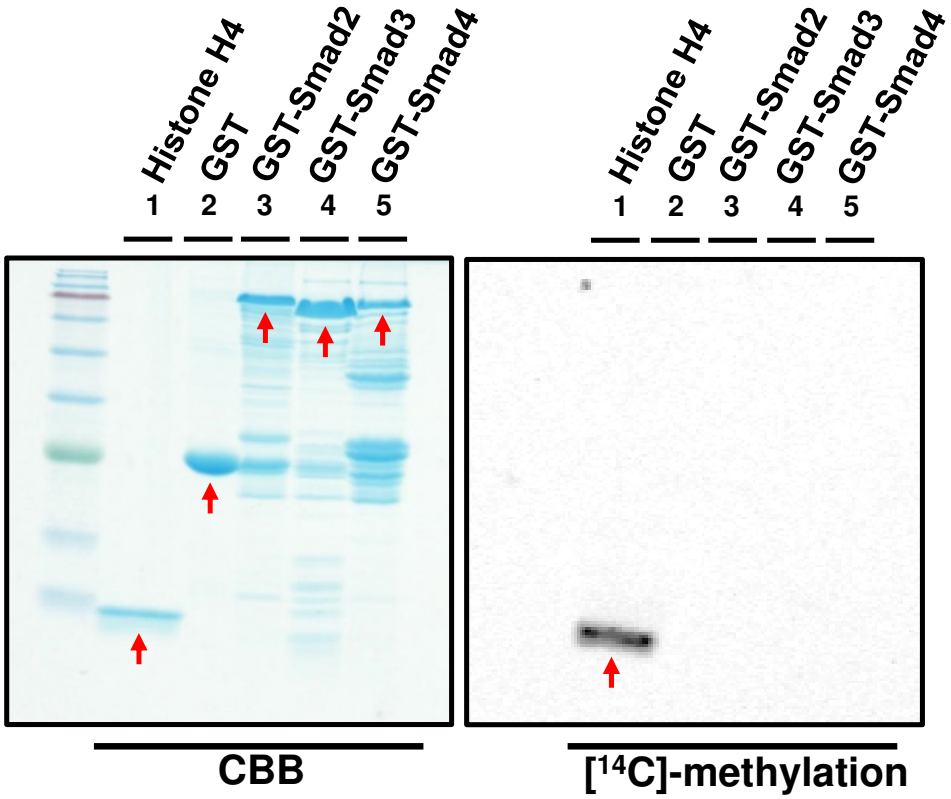
Supplementary Figure 6

Primary cultured cardiac fibroblasts from neonatal rats were treated with the PRMT5 inhibitor EPZ015666 at the indicated concentration and then stimulated with or without TGF-β (10 ng/mL). [^{3}H]-labeled L-proline uptake by the cells was measured after incubation for 48 h. Values are presented as mean ± SD. One-way ANOVA, followed by Dunnett test versus TGF-β treated group (A). *Prmt5* knockdown was confirmed in primary cultured cardiac fibroblasts by western blotting and quantitative PCR. Values are presented as mean ± SD. Student's *t*-test.* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

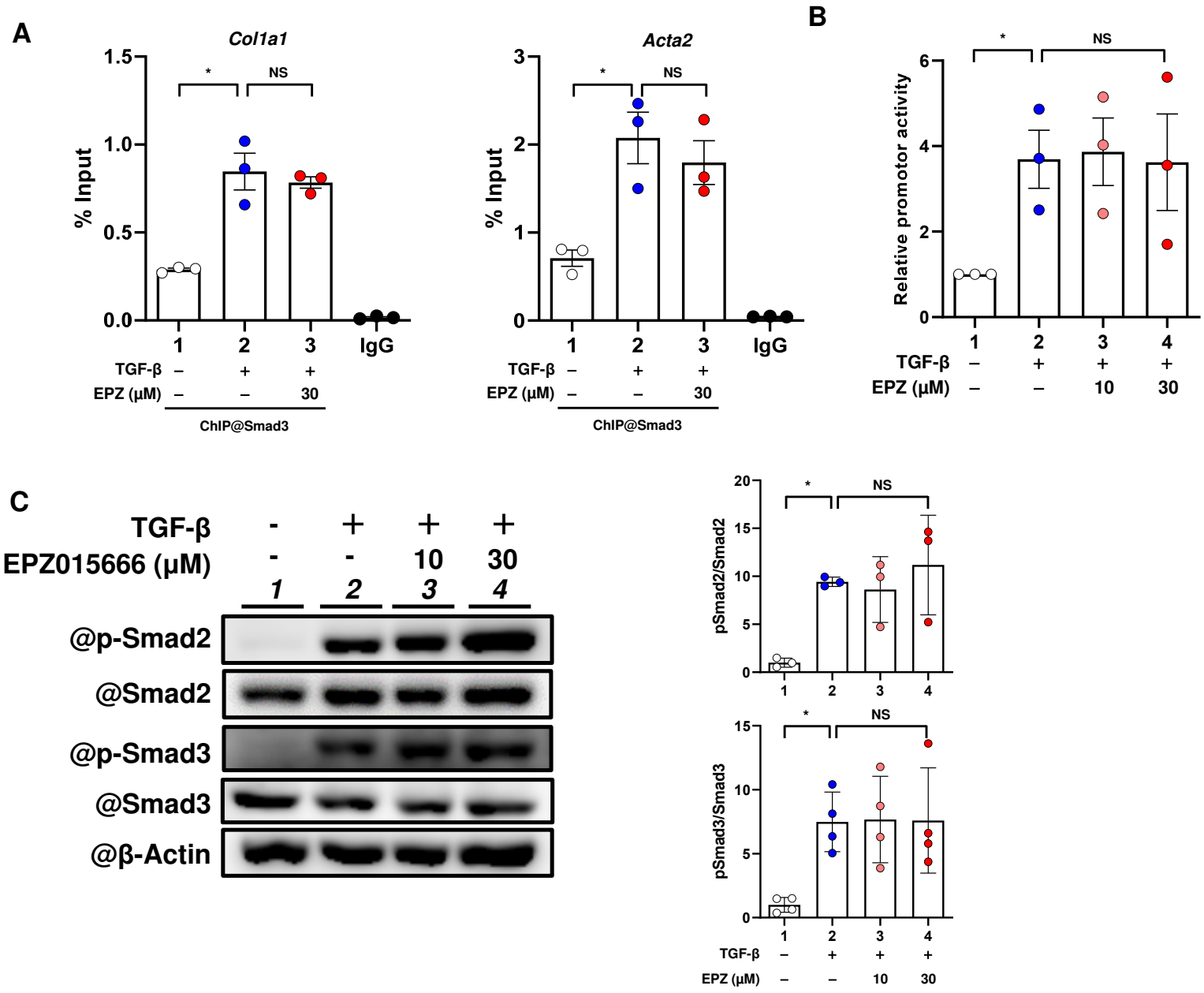


Supplementary Figure 7

Primary cultured cardiac fibroblasts from neonatal rats were stimulated with TGF-β (10 ng/mL) in the presence or absence of the PRMT5 inhibitor EPZ015666 (10 μM or 30 μM). Protein expression levels of SDMA (A, B) and H3R2me2s (C, D) were examined by western blotting. Band density was measured with ImageJ software. Values are presented as mean ± SD (n = 3-6 experiments). One-way ANOVA, followed by Tukey's multiple-comparisons test. * $p < 0.05$. NS: no significant difference.

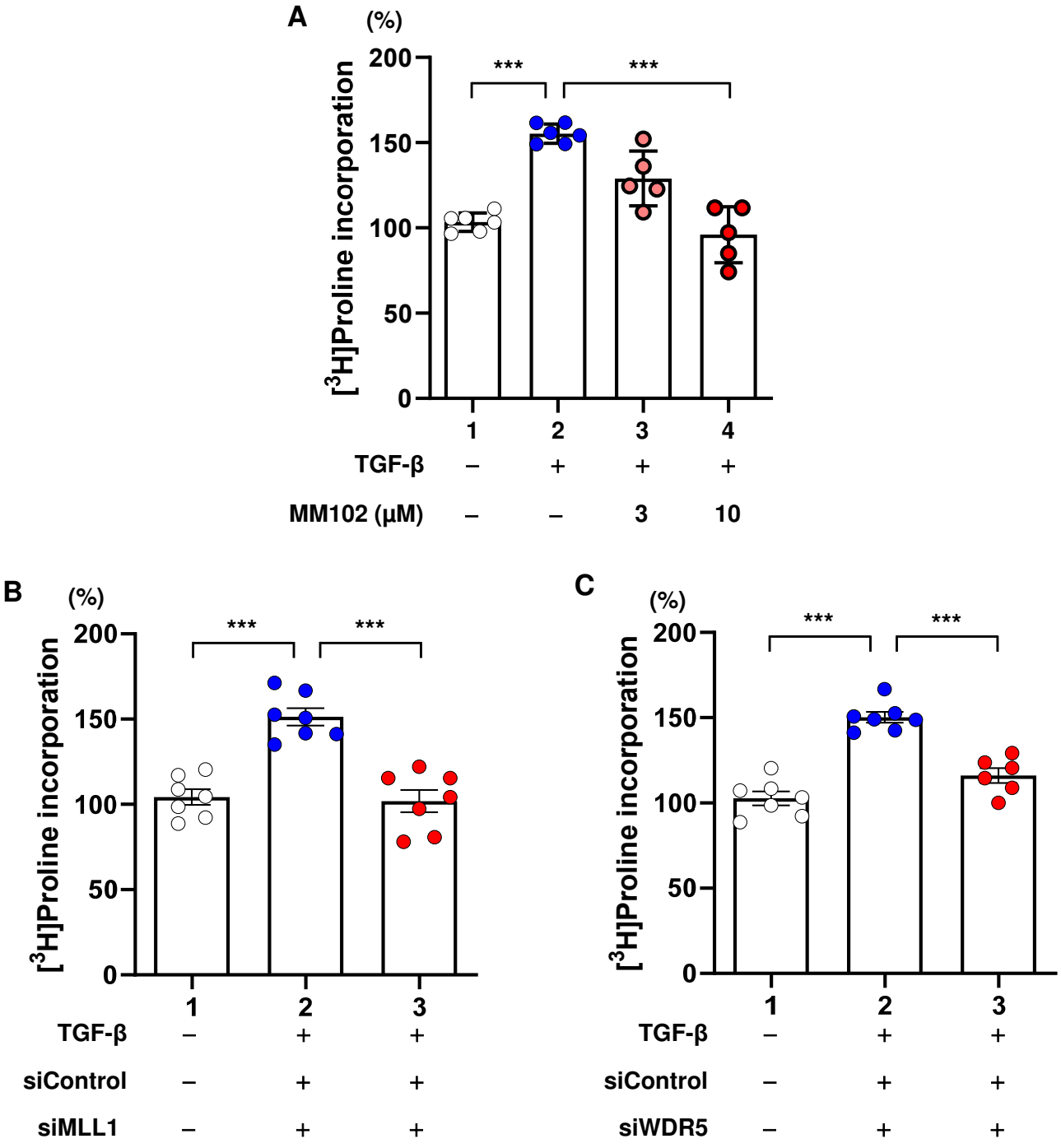


Supplementary Figure 8
PRMT5 does not methylate Smad2, Smad3, or Smad4. Recombinant histone 4 (lane 1) and purified GST-fusion proteins (lane 2-5) were added to the recombinant Flag-PRMT5/MEP50 complex and [^{14}C]-SAM and then incubated at 30 ºC for 120 min. The samples were separated by SDS-PAGE and stained with CBB after membrane transfer. After exposure to the imaging plate, autoradiography was detected with a Typhoon 9400 imager. Left panel: CBB staining; band positions of each protein and histone 4 are shown by the red arrows. Right panel: autoradiography.



Supplementary Figure 9

The PRMT5 inhibitor EPZ015666 does not suppress activation of the TGF-β/Smad pathway in cardiac fibroblasts. Primary cultured cardiac fibroblasts from neonatal rats were stimulated with TGF-β (10 ng/mL) in the presence of EPZ015666 (30 μM) for 2 h. ChIP qPCR assays were performed with anti-Smad3 antibody and ChIP primers for Col1A1 and Acta2 (A). Primary cultured cardiac fibroblasts were transfected with SBE4-luc and then stimulated with TGF-β (10 ng/mL) in the presence of EPZ015666 for 24 h. The cells were then lysed and transcriptional activity was measured by dual reporter assay (B). Primary cultured cardiac fibroblasts were stimulated with TGF-β in the presence of EPZ015666. Phosphorylation of Smad2/3 was examined by western blotting (C). Values are presented as mean ± SD. One-way ANOVA, followed by Tukey's multiple-comparisons test. * $p < 0.05$. NS: no significant difference.



Supplementary Figure 10

Primary cultured cardiac fibroblasts from neonatal rats were treated with the histone methyltransferase inhibitor MM102 at the indicated concentration and then stimulated with or without TGF-β (10 ng/mL) (A). The cells were transfected with siRNA (siControl, siWDR5, or siMLL1) and then stimulated with or without TGF-β (B, C). [^{3}H]-labeled L-proline uptake by the cells was measured after incubation for 48 h. Values are presented as mean ± SD (n = 5-7). One-way ANOVA, followed by Tukey's multiple-comparisons test. *** $p < 0.001$.