Supplementary Figures



Figure S1. Isolation of genetically-defined SMCs. $mT/mG.Myh11-CreER^{T2}$. $Tgfbr2^{i/f}$ mice were treated with tamoxifen for 5 d starting at 4 wk of age and the thoracic aorta was harvested at 8 wk. The adventitia and endothelium were sharply removed under magnification and the medial cells were isolated after enzymatic digestion. (*A*) Using conventional SMC isolation techniques, GFP⁺ cells were contaminated with a minor population of RFP⁺ cells that tended to overgrow the cultures. After sorting by flow cytometry, a highly purified population of GFP⁺ cells was obtained without later emergence of RFP⁺ cells. Bar=100 µm. (*B*) Representative dot plot showing that 85% of cells were GFP⁺ at the time of sorting and 15% were RFP⁺ that included either non-recombined medial cells or contaminating intimal and adventitial cells. (*C*) Histogram showing % GFP⁺ and RFP⁺ cells averaged from 5 independent isolations.



Figure S2. Aortic pathology after *Tgfbr2* disruption. *Myh11-CreER^{T2}*. *Tgfbr2^{t/f}* mice were treated with tamoxifen or vehicle at 4 wk of age (unless otherwise specified) and the thoracic aortas were subsequently analyzed. (*A*) Initiation site and extent of aortic dissections (arrows) at 8 wk (induced at 4 wk) vs. 13 wk (induced at 9 wk of age). (*B*) Obvious false lumen containing blood (arrows) at 8 wk caused by marked separation of elastic laminae. (*C*) Immunohistochemistry for leukocyte common marker, CD45 demonstrated numerous infiltrating cells (arrows) in the adventitia, but not the media, of dissected aortas at 10 wk. (*D*) Immunolabeling for erythroid lineage marker, TER119 and smooth muscle marker, SMA showed many red blood cells within the elastic lamina (arrow) and focal areas of the media devoid of SMCs (arrow) in dissected aortas at 10 wk. (*E*) EVG stains show similar abnormalities of medial hematomas, elastin fragmentation, and elastic lamina widening in both ascending and descending thoracic aorta at 8 wk. (*F*) Extreme degree of medial degeneration with focal areas of vessel wall consisting only of fibrotic adventitia (arrows) at 30 wk. Bars=100 μm.



Figure S3. Delayed vascular pathology in the absence of dissection. *Myh11-CreER*^{T2}.*Tgfbr2*^{*f/f*} mice were treated with vehicle or tamoxifen at 4 wk of age and ascending thoracic aortas without mural hematomas were subsequently analyzed. (*A*) H&E, EVG, and trichrome stains showed relatively normal histological appearance at 10 wk, (*B*) but evidence of elastin fragmentation, elastic lamina widening, and adventitial fibrosis contributing to mural thickening by 30 wk of age. Bars=100 µm.



Figure S4. T β RII inactivation in SMCs increases the production of extracellular matrix molecules and TGF- β ligand. Quantitative RT-PCR of thoracic aortas from 6 wk old vehicle- or tamoxifen-treated *Myh11-CreER*^{T2}. *Tgfbr2*^{t/f} mice for (**A**) Col1a1, Col3a1, Thbs1, (**B**) Tgfb1, Tgfb2, and Tgfb3 transcripts; *n*=3-9 pooled from 3 separate experiments; **P*<0.05, ***P*<0.01, and *****P*<0.001, t-test.



Figure S5. Serologic neutralization of TGF- β after *Tqfbr2* disruption in SMCs does not rescue the aortic dissection phenotype, but prevents adventitial thickening and precipitates fatal aortic rupture. *Myh11-CreER*⁷². *Tqfbr2*^{t/f} mice were treated with tamoxifen at 4 wk of age for 5 d and either neutralizing monoclonal antibody (mAb) to TGF- β 1, -2, -3 or irrelevant IgG1 at 250 µg i.p., every other day, from 4-8 wk. (A) Representative EVG stains of ascending thoracic aortas showing adventitial collagen (red-purple color, arrows) with higher magnification shown in insets; bars=100 μ m with (**B**) mean adventitial thickness of ascending and descending aortas; n=8 lgG and n=14 mAb, *P<0.05, **P<0.01, t-test. (**C**) Representative Sirius Red stains of ascending thoracic aortas showing adventitial collagen (dark red color, arrows); bar=100 µm with (**D**) intensity of Sirius Red signal in adventitia and media of ascending aortas; $n=7 \log a$ and n=8 mAb, *P<0.05, t-test. (E) Aortic dissection rates of mAb- vs. IgG-treated (littermate controls) or untreated (historical controls) Tafbr2 KO mice (11/14 vs. 5/8 vs. 19/40, respectively; P=0.1219, chi-square test) and survival rates of mAb- vs. IgG-treated or untreated Tgfbr2 KO mice (11/14 vs. 8/8 vs. 40/40, respectively; P=0.0063, logrank test) at 8 wk of age. (F) Post-mortem of mAb-treated mouse at 7 wk showing intra-thoracic blood clot (arrow, left panel), mediastinal hematoma overlying proximal aorta (arrow, middle panel), and free rupture of the underlying ascending aorta (arrow, right panel).



Figure S6. Changes in TGF- β signaling after T β RII inactivation. (*A*) Immunoblotting for phospho-Smad2, phospho-p38, phospho-ERK1/2, and phospho-S6K in thoracic aortas from vehicle-treated *Myh11-CreER*^{T2}. *Tgfbr2*^{*ff*} (WT) or tamoxifen-treated *Myh11-CreER*^{T2}. *Tgfbr2*^{*wtf*} (Het) and *Myh11-CreER*^{T2}. *Tgfbr2*^{*ff*} (Homo) mice at 6 wk. (*B*) Immunofluorescence microscopy for expression of phospho-Smad2 (green color as indicated by arrow with blue color for DAPI labeling of nuclei and red autofluorescence of elastic lamina delineating the media in the upper two panels) and phospho-ERK1/2 (red color as indicated by arrow with blue color for DAPI labeling of nuclei and green autofluorescence of elastic lamina delineating the media in the lower two panels) in the thoracic aorta wall of vehicle- or tamoxifen-treated *Myh11-CreER*^{T2}. *Tgfbr2*^{*ff*} mice at 10 wk; bar=30 µm.



Figure S7. Serologic neutralization of TGF- β does not further inhibit Smad2 phosphorylation nor prevent MAPK activation in KO aorta. (*A*) Representative immunoblotting and (*B*) relative expression of phosphorylated (p-) to total Smad2, p38, and ERK1/2 in thoracic aortas from *Myh11-CreER*^{T2}. *Tgfbr2*^{*i*/f} mice treated with tamoxifen at 4 wk for 5 d and either neutralizing monoclonal antibody (mAb) to TGF- β 1, -2, -3 or irrelevant IgG1 at 250 µg i.p., q.o.d., from 4-6 wk; *n*=6; *P*=0.7025 for p-Smad2, *P*=0.1755 for p-p38, *P*=7853 for p-ERK1/2, t-test.



Figure S8. Disruption of T β RII in cultured SMCs prevents signaling to multiple TGF- β isoforms. (*A*) Immunoblotting for phosphorylated (p-) and total Smad2, p38, and ERK1/2 in purified GFP⁺ SMCs isolated from the thoracic aortas of tamoxifen-induced *mT/mG.Myh11-CreER*^{T2} (Cre) and *mT/mG.Myh11-CreER*^{T2}. *Tgfbr2*^{*ff*} (KO) mice, serum-deprived for 24 h, and then treated with TGF- β 2 at 1 ng/mL or (*B*) TGF- β 3 at 1 ng/mL for 0-180 min.



Figure S9. Changes in smooth muscle contractile proteins after TβRII inactivation. (*A*) Immunoblotting for SMA, SM22, and SMMHC in thoracic aortas from vehicle-treated *Myh11-CreER*^{T2}.*Tgfbr2*^{t/f} (WT) or tamoxifen-treated *Myh11-CreER*^{T2}.*Tgfbr2*^{wt/f} (Het) and *Myh11-CreER*^{T2}.*Tgfbr2*^{t/f} (Homo) mice at 6 wk. (*B*) Immunofluorescence microscopy for phospho-MLC (red color) and SMA (green color) with merged images including DAPI labeling of nuclei (blue color) in the aortic wall of vehicle- or tamoxifen-treated *Myh11-CreER*^{T2}.*Tgfbr2*^{t/f} mice at 10 wk; bar=30 µm.



Figure S10. Shift from contractile to proliferative phenotype after *Tgfbr2* disruption. SMCs were cultured from the thoracic aortas of tamoxifen-induced *mT/mG.Myh11-CreER*^{T2} (Cre) or *mT/mG.Myh11-CreER*^{T2}. *Tgfbr2*^{*f/f*} (KO) mice. (*A*) Appearance of flow cytometry-selected GFP⁺ (green color) cells at passage 6; bar=100 µm. Immunofluorescence analysis for (*B*) SM22 and (*C*) SMA expression (red color); bars=30 µm. (*D*) SMCs were plated at 1×10^4 cells/mm² in serum-supplemented Claycomb medium, cultured for 24 h, then BrdU was added at 1 mM for 24 h, and its incorporation in fixed permeabilized cells was assessed by immunohistochemistry (brown color, nuclei counter-stained with hematoxylin); bar=100 µm.



Figure S11. Delayed mTOR signaling by TGF-β and effects of mTOR inhibition on IGF1 signaling. (*A*) Immunoblotting for phospho- and total S6K and S6 in aortic GFP⁺ SMCs from tamoxifen-induced *mT/mG.Myh11-CreER*^{T2} (Cre) or *mT/mG.Myh11-CreER*^{T2}.*Tgfbr2*^{t/f} (KO) mice, serum-deprived for 24 h, and then treated with TGF-β1 at 1 ng/mL for 0-180 min. Increased activation of mTOR mediators (S6K and S6) is evident at 180 min only in TβRII-expressing (Cre) SMCs. (*B*) Immunoblotting for phospho-S6K, phospho-ERK1/2, and phospho-AKT in aortic GFP⁺ SMCs lacking TβRII from KO mice, serum-deprived for 24 h, pretreated with rapamycin at 0-100 ng/mL for 60 min and then treated with IGF1 at 0-100 ng/mL for 10 min. Only IGF1 signaling mediators downstream of mTOR (S6K) are inhibited by rapamycin.



Figure S12. Rapamycin maintains a quiescent SMC phenotype. Thoracic aortas were analyzed from *Myh11-CreER*⁷². *Tgfbr2*^{*ff*} mice treated with vehicle or tamoxifen ± rapamycin at 2 mg/kg/d i.p. q.d. from 3-7 wk. (*A*) Immunoblotting for phospho-Smad2 and -p38. (*B*) H&E stains showing nuclei (blue color, arrows); bar=100 µm. (*C*) Number of medial nuclei per mm² or per cross-section (x-sec), media and adventitia areas; *n*=6, **P*<0.05, ***P*<0.01, ****P*<0.001, one-way ANOVA. (*D*) qPCR for transcript expression of proliferative marker (Mki67), cell cycle regulators (Ccna2, Ccnb2), growth factor (Igf1), and contractile molecules (Acta2, TagIn, Myh11); *n*=6, **P*<0.05, ****P*<0.001, one-way ANOVA. (*E*) Immunoblotting for phospho-MLC and MLC. (*F*) Immunohistochemistry for CD45 (inset: spleen as positive control) showing similar sparse leukocytes in adventitia of untreated and treated groups (*n*=6, *P*=0.1311, one-way ANOVA) and uniformly absent medial infiltrates; bar=100 µm.



Figure S13. TβRII inactivation in smooth muscle exacerbates aortic medial degeneration induced by mutant fibrillin-1. (*A*) H&E, EVG, and trichrome stains of ascending thoracic aortas from 8 wk old $Fbn1^{C1039G/+}$.*Myh11-CreER*^{T2}.*Tgfbr2*^{f/f} mice showed greater elastin disruption, increased adventitial fibrosis, and thicker vessel walls after tamoxifen than vehicle treatment at 4 wk of age. (*B*) Similarly, histological analysis at 30 wk of age showed greater pathological changes of the aorta following *Tgfbr2* disruption on *Fbn1*^{C1039G/+} background than due to mutant *Fbn1* alone. Bars=100 µm.



Figure S14. Effects of T β RII inactivation and/or fibrillin-1 mutation in thoracic aorta at 5-8 wk of age. *Myh11-CreER*^{T2}. *Tgfbr2*^{*ff*} (abbreviated as *Cre.Tgfbr2*) mice were cross-bred to *Fbn1*^{*C1039G/+*} (abbreviated as *Fbn1*) mice, treated with vehicle or tamoxifen for 5 d starting at 4 wk, and their aortas were analyzed at various ages. (*A*) Immunoblotting for phospho- and total S6K and S6 in thoracic aortas at 5 wk. (*B*) Microarray expression data (in arbitrary units) for growth factor, proliferative marker, and cell cycle regulators in thoracic aortas at 6 wk; *n*=3, ****P*<0.001, one-way ANOVA. (*C*) Immunofluorescence analysis for the proliferative marker, Ki-67 (red color) and the smooth muscle marker, SMA (green color) in thoracic aortas at 8 wk; bar=50 µm. Signaling and expression changes (increased p-S6K and p-S6, increased Igf1, increased proliferation markers and cell cycle regulators) characteristic of *Tgfbr2* deletion in aortic smooth muscle were not greater in compound mutant animals.



Figure S15. Effects of T β RII inactivation and/or fibrillin-1 mutation on thoracic aorta at 30 wk of age. *Myh11-CreER*^{T2}. *Tgfbr2*^{f/f} (abbreviated as *Cre.Tgfbr2*) mice were cross-bred to *Fbn1*^{C1039G/+} mice, treated with vehicle or tamoxifen for 5 d starting at 4 wk, and their thoracic aortas were procured at 30 wk. Immunohistochemical analysis for (*A*) phospho-Smad2, (*B*) phospho-S6K, (*C*) phospho-MLC, and (*D*) SMA; protein detection indicated by brown color, bars=100 µm. Signaling and expression changes (decreased p-Smad2, increased p-S6K, decreased p-MLC, and decreased SMA) characteristic of *Tgfbr2* deletion in aortic smooth muscle were not greater in compound mutant animals.

Transcript Gene Fold-Δ P-value FDR adj. Mean Mean Mean Veh Veh Tmx T ID assigned symbol Tmx/Veh Tmx/Veh P-value Veh Tmx 1 2 3 4 10414262 NM_00789 Ear2 4.77 0.000224 0.000379 167.2 798.0 172 138 197 628 6 10496727 NM_002699 Ddah1 4.59 0.000093 0.00204 329.2 1510.2 277 309 417 1607 1* 10523717 NM_00926 Spp1 4.16 0.001223 0.001646 185.6 771.9 200 278 115 1043 6 10379535 NM_02144 Ccl8 3.66 0.00009 0.000379 2822.6 10246.9 2399 2989 3136 10372 88 10499189 NM_03070 Fcrls 3.55 0.000000 0.00007 374.6	IX Tmx 5 6 11 1243 37 1837 7 715 7 574 22 11562 20 1414 23 845 4 895 32 1575 32 5175
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Transcript	Gene	Gene	Fold-∆	P-value	FDR adj.	Mean	Mean	Veh	Veh	Veh	Tmx	Tmx	Tmx
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10372652	NM_013590	Lyz1	2.20	0.000170	0.000305	463.6	1021.8	413	565	427	934	921	1240
10594251	NM_024245	Kif23	2.20	0.000118	0.000241	198.0	435.4	210	168	219	403	398	514
10462796	NM_010615	Kif11	2.16	0.000072	0.000170	191.6	414.2	188	191	195	408	392	444
10436095	NM_020509	Retnla	2.16	0.016799	0.018666	271.3	586.1	215	230	402	443	505	901
10424543	NM_018865	Wisp1	2.15	0.000032	0.000119	387.7	834.1	369	351	450	801	874	828
10389214	NM_011338	Ccl9	2.15	0.000119	0.000241	504.4	1082.2	514	462	540	1044	1064	1140
10396952	NM_001033	Ttc9	2.12	0.002102	0.002675	458.6	974.4	384	544	462	758	850	1434
10517517	NM_007572	C1qa	2.12	0.000012	0.000056	956.9	2028.5	911	914	1052	2024	1850	2229
10360391	NM_00104	lfi203	2.11	0.008569	0.010054	462.6	978.3	440	404	558	1416	627	1054
10526783	NM_001013	BC055004	2.11	0.000128	0.000252	143.1	302.1	126	152	153	279	394	250
10603551	NM_007807	Cybb	2.11	0.000030	0.000115	889.3	1876.7	887	910	871	2292	1505	1916
10444291	NM_207105	H2-Ab1	2.11	0.000717	0.001003	1173.6	2473.3	1130	1362	1050	2364	2178	2938
10605815	NM_080858	Asb12	2.11	0.000225	0.000379	172.9	363.9	187	139	200	436	370	299
10387536	NM_009853	Cd68	2.10	0.000192	0.000337	827.6	1737.4	670	844	1002	1763	1509	1971
10587854	NM_177909	SIc9a9	2.09	0.000160	0.000294	467.1	977.9	437	433	539	859	895	1215
10360040	NM_010188	Fcgr3	2.09	0.000000	0.000007	444.4	929.0	421	452	461	934	915	938
10502565	NM_03060 ⁻	Clca2	2.09	0.005716	0.007019	111.1	232.1	80	137	124	296	239	177
10581013	NM_009866	Cdh11	2.09	0.000125	0.000249	1609.7	3363.2	1825	1769	1292	3157	3419	3524
10377405	NM_011496	Aurkb	2.07	0.000054	0.000139	366.8	760.8	354	380	367	698	743	850
10450242	NM_009780	C4b	2.07	0.000009	0.000044	1451.5	3009.5	1413	1386	1561	2949	3144	2940
10466190	ENSMUST	Ms4a14	2.06	0.000387	0.000589	87.7	181.0	97	79	88	213	157	178
10462623	NM_008337	lfit1	2.06	0.035871	0.038630	356.0	734.3	310	287	509	1366	503	576
10363082	NM_013532	Lilrb4	2.06	0.000019	0.000079	295.4	607.6	253	336	303	701	542	591
10454709	NM_009004	Kif20a	2.06	0.001691	0.002254	178.3	366.7	173	183	179	331	332	449
10428370	NM_175456	Abra	2.05	0.006738	0.008063	964.7	1976.3	936	1200	800	2026	2572	1481
10557862	NM_001082	ltgam	2.05	0.000000	0.000007	265.0	542.5	252	279	264	567	534	527
10508663	NM_010686	Laptm5	2.04	0.000005	0.000031	1703.4	3479.6	1568	1808	1743	3597	3278	3573
10487340	NM_144818	Ncaph	2.04	0.000000	0.000007	193.3	393.5	201	195	185	379	384	419
10557156	NM_01112 ²	Plk1	2.03	0.000061	0.000149	337.8	687.2	334	344	335	656	637	776
10416437	NM_008879	Lcp1	2.03	0.000040	0.000125	618.8	1254.7	586	682	593	1516	1114	1170
10411082	NM_011582	Thbs4	2.02	0.003950	0.004894	353.9	716.3	317	490	285	759	717	675
10408077	NM_178183	Hist1h2ak	2.02	0.000075	0.000173	1260.4	2547.2	1205	1443	1152	2429	2292	2969
10407126	NM_152804	Plk2	2.02	0.000119	0.000241	191.7	387.0	209	214	158	412	353	399
10434689	NM_01346	Ahsg	2.02	0.006869	0.008149	1147.1	2313.9	1284	1327	885	2678	1676	2760
10517513	NM_007574	C1qc	2.01	0.000469	0.000691	1664.0	3342.5	1402	1572	2090	3451	3146	3440
10485982	NM_009608	Actc1	2.01	0.014288	0.016003	1030.5	2067.5	809	950	1424	2550	1687	2055
10478048	NM_008489	Lbp	2.01	0.000095	0.000204	1402.1	2813.0	1382	1268	1573	2393	3145	2958
10438784	BC086669	Gm606	-2.09	0.000729	0.001010	621.6	298.1	635	697	542	287	323	286
10571297	ENSMUST	Gm9951	-2.11	0.000001	0.000010	699.3	331.8	734	647	720	325	317	354
10600886	NM_029536	Gpr165	-2.11	0.000383	0.000589	1288.6	610.2	1597	1316	1018	714	627	508
10523506	NM_173404	Bmp3	-2.17	0.000148	0.000276	2631.4	1214.5	2694	2481	2726	1094	1308	1252
10382692	BC065414	2210020M0	-2.18	0.000043	0.000125	682.7	313.6	742	707	607	317	350	278
10447860	NM_001034	Pnldc1	-2.24	0.000001	0.000010	768.9	342.9	674	804	840	327	358	344
10439321	NM_021301	Slc15a2	-2.28	0.019590	0.021595	349.5	153.1	293	460	317	207	144	120
10408543	ENSMUST	Mylk4	-2.48	0.000000	0.000007	10998.4	4438.9	11073	10860	11063	4528	4695	4115
10356154	NM_172430	Sphkap	-2.49	0.008617	0.010054	1038.1	416.5	1113	1676	600	448	525	307
10554249	NM_007424	Acan	-2.53	0.000500	0.000721	2144.5	849.0	1982	2690	1850	897	885	771