Supplementary Materials:

Supplemental Table S1. Effect of rapamycin on AD incidence.

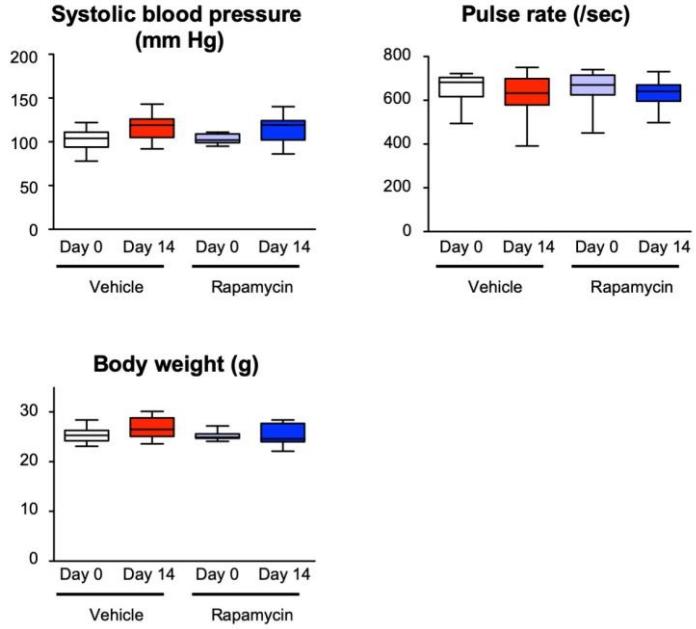
	BA+DMSO	BA+Rapa
AD +	25	3
AD –	11	12
Total	36	15
Incidence (%)	69.4	20.0

$p < 0.01$ by Fisher's exact test

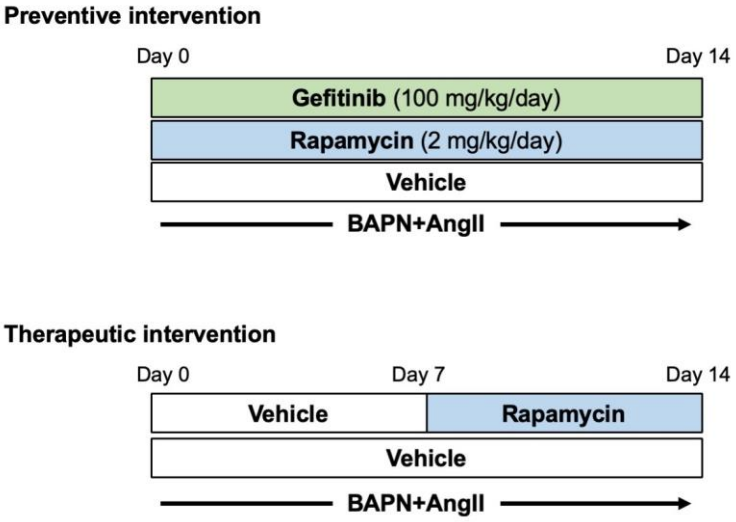
Supplemental Table S2. Genes in Subnetworks #1 – #3.

Subnetwork #1									
Adam12	Adgre1	Adm	Aldh1b1	Aldh2	Aqp5	Asf1b	Asns	Atp6v1g2	Aurka
Batf	Birc2	Birc5	Ccl2	Ccna2	Ccnb1	Ccnb2	Ccne1	Ccnf	Cd68
Cdc20	Cdca3	Cdca5	Cdca8	Cdkn2a	Cdt1	Cenpa	Cenpe	Cenpi	Cenpk
Cgref1	Chaf1b	Cidea	Creb3l3	Cxxc4	Diras2	E2f1	E2f2	Ebi3	Eme1
Epha1	Faim2	Fam111a		Fanca	Fen1	Fes	Fn3k	Foxm1	Fscn1
Gale	Garem	Gdf6	Gp49a	Gpr39	Gstm1	Has1	Hist1h1b	Hist1h2ab	Hist1h2ag
Hist1h2ah	Hist1h2ak	Hist1h2an		Hist1h2ao		Hmga1	Hyal1	Ifi205	Igf1
Kif20a	Kif22	Klhl38	Lrr1	Lsmem2	Mapk11	Mcm10	Mcm5	Mki67	Mlkl
Murc	Mybl2	Ncaph	Ngf	Nr4a1	Nsl1	Nusap1	Optc	Osr2	Pdzrn4
Pidd1	Plk1	Pole	Prc1	Prkar1a	Psat1	Psrc1	Ptger1	Ptgs2	Racgap1
Rad51ap1	Rfx2	Rrm2	Sapcd2	Sgol1	Sh3rf2	Slc14a2	Slc17a9	Slc25a22	Slc25a34
Sost	Spc25	Stmn1	Tacc3	Thbs1	Tk1	Tmtc2	Tnfaip8l1	Tnfrsf23	Tpx2
Traip	Trip13	Ube2c	Uhrf1	Vstm4	Wisp1				
Subnetwork #2									
Adam11	Adam8	Adamts4		Adgre1	Adora2b	Aif1	Alas2	Alox5ap	Alpl
Ambp	Anxa8	Apoc2	B4galnt1	Batf	Bcl2a1d	Bcl3	Begain	Bhlhe40	Blnk
Bmper	Btk	Bves	C1qa	C1qb	C1qc	C5ar1	Ccdc88b	Ccl12	Ccl2
Ccl6	Ccl7	Ccl8	Ccl9	Ccr2	Ccr5	Cd209a	Cd5	Cd52	Cd72
Cfp	Ch25h	Chil3	Clec4a1	Clec4d	Clec4n	Cmpk2	Col8a1	Coro1a	Cotl
Csf2rb	Csf2rb2	Cthrc1	Ctss	Cx3cr1	Cxcl14	Cysltr1	Cyth4	Dbp	Dclk1
Ddah1	Dok2	Dpep2	Dusp8	Ear10	Ear2	Fam180a	Fcer1g	Fcgr1	Fcgr2b
Fcgr4	Fcrls	Fes	Ffar2	Fgd3	Fst	Gda	Gng2	Gp49a	Gpr132
Gpr35	Gpr65	Grem2	H19	Hck	Hdac11	Hk3	Hmga1	Hp	Ifi27l2a
Ifit3	Ifitm6	Ihh	Il11	Il1b	Il33	Il4ra	Itga6	Itgb2	Itgb7
Jun	Kcnc4	Kctd16	Kng1	Krtap11-1		Laptm5	Lat2	Lcp1	Lgals3bp
Lgi3	Lilra6	Lilrb4	Lpxn	Lrg1	Lrmp	Lrrc25	Ltb4r1	Lyz1	Meox1
Mmp19	Ms4a6c	Ms4a6d	Ms4a7	Msr1	Myo1f	Myo1g	Ncam1	Ncf1	Ncf4
Nfam1	Nrros	Oas1a	Oas1f	Oasl1	Pabpc1l	Panx1	Pappa2	Pde10a	Pdpn
Pgc	Piezo2	Pik3r5	Pilra	Pira11	Pira6	Pira7	Pirb	Pitpnm3	Plac8
Plbd1	Pld4	Prg4	Ptpn6	Ptpn7	Ptx3	Rab26	Rac2	Rbm24	Retnla
Rnase2a	Rps6ka1	S1pr3	Saa3	Satb1	Selplg	Serinc2	Serpina3g	Serpina3n	
Serpinb1a		Sfmbt2	Sh2b2	Siglec1	Sirpb1a	Slc13a3	Slc15a3	Slc16a6	Slc2a6
Slc38a11	Slc40a1	Slfn2	Snx20	Soat2	Tcap	Timp1	Tlr1	Tmem173	Tmem37
Tnfaip2	Tnfaip8l2	Tnfrsf11b		Tnfsf15	Tnni2	Tpbg	Trem2	Treml1	Ttc9
Tubb3	Tyrobp	Ubash3b		Ucp2	Ucp3	Upp1	Vav1	Vsig4	Wfdc17
Wfdc21	Wnk2	Zbp1							
Subnetwork #3									
Aass	Ackr4	Acyp1	Adcyap1	Adra1b	Aff3	Ak4	Akap7	Aldh1a2	Aldh6a1
Amd-ps5	Anapc15	Arid3a	Atg9b	Bloc1s3	Cabp5	Calcoco2	Camsap2	Card6	Cat
Catsper4	Ccdc172	Cd209f	Cd209g	Cd22	Cd300ld2	Cd300lf	Cd300lh	Cdc27	Cdnf
Cep295	Cftr	Chat	Chst4	Chsy3	Clstn3	Cmah	Cmya5	Cnr1	Col15a1
Coro6	Cped1	Crispld1		Crnde	Csrnp3	Cuedc1	Cwc22	Cyp17a1	Cystm1
Dcaf12l2	Dcbld2	Ddx25	Defb28	Dlg2	Dmkn	Duoxa1	Dusp7	Dync1i1	E4f1
Egln3	Elf4	Fam107a		Fam135a	Fam13c	Fam19a3	Fam210a	Fbxo40	Fgfr4
Fmn2	Fmr1nb	Folr1	Fyttd1	Gabra2	Gata4	Gbp6	Gbx1	Gclm	Git2
Gmpr	Gnal	Gpr153	Grb10	Grifin	H1foo	H1fx	Hap1	Hdc	Hebp2
Herc2	Ifna11	Il18r1	Iqcf4	Iqcg	Iqsec3	Klk12	Klra1	Klra22	Klra7
Kmt2d	Knstrn	Krt19	Krt8	Krtap19-4		Kxd1	Lgals2	Lhx1os	Limk1
Lrrc2	Lrrc8b	Lrrn4	Lyplal1	Lzts3	Map7	Mapt	Mast3	Maz	Mbtd1
Med1	Micall2	Mme	Mrgprg	Ms4a5	Msln	Mt3	Mthfs	Mtpn	Mybphl

Myo18b	N6amt1	Nanog	Nav2	Neb	Nkx2-3	Nog	Notch1	Nr1i3	Oacyl
Olfr1500	P2ry14	Pabpc1l2a-ps		Pabpc1l2b-ps		Pabpc4	Pabpc6	Pak6	Pdik1l
Pdzrn3	Pif1	Pign	Pik3c2b	Pinx1	Pitpnc1	Plekhh2	Plet1	Plp1	Pnma2
Podn	Ppapdc2	Prex2	Prr3	Ptk7	Rab26os	Rabgap1	Rabif	Ranbp17	Rasal3
Rbm15b	Rergl	Rhox3a	Ripk2	Rnf141	Rnf165	Rnf219	Rnu2-10	Rnu3b1	Rpp40
Rprl2	Rs1	Rsph4a	Rspo3	Scn3b	Serpini1	Sgcd	Shank2	Shc4	Slc25a16
Slc35d1	Slc35e2	Slc35g1	Slpi	Snora74a	Sowahb	Sox1	Spata24	Srbd1	Src
Srgap3	Srp54b	Srsf11	Ssfa2	St6galnac1		Suv39h1	Syn3	Tbx22	Tcf3
Tcof1	Tdgf1	Tgfbrap1		Tle4	Tlr12	Tmed7	Tmem126b	Tmem170b	
Tmem55a	Tmem56	Tmem59l		Tmprss11b		Tnc	Tnfaip8	Triobp	Trmt6
Trp63	Trpm1	Tulp1	Txlnb	Ucp1	Upk1b	Usp22	Usp36	Usp6nl	Usp8
Utp15	Vav2	Vmn1r87		Vpreb2	Wdr38	Wdr54	Wee1	Wfdc13	Wnt6
Xk	Xpo4	Yy2	Zdhhc2	Zfhx2	Zfp691	Zfp740	Zfp790	Zswim4	

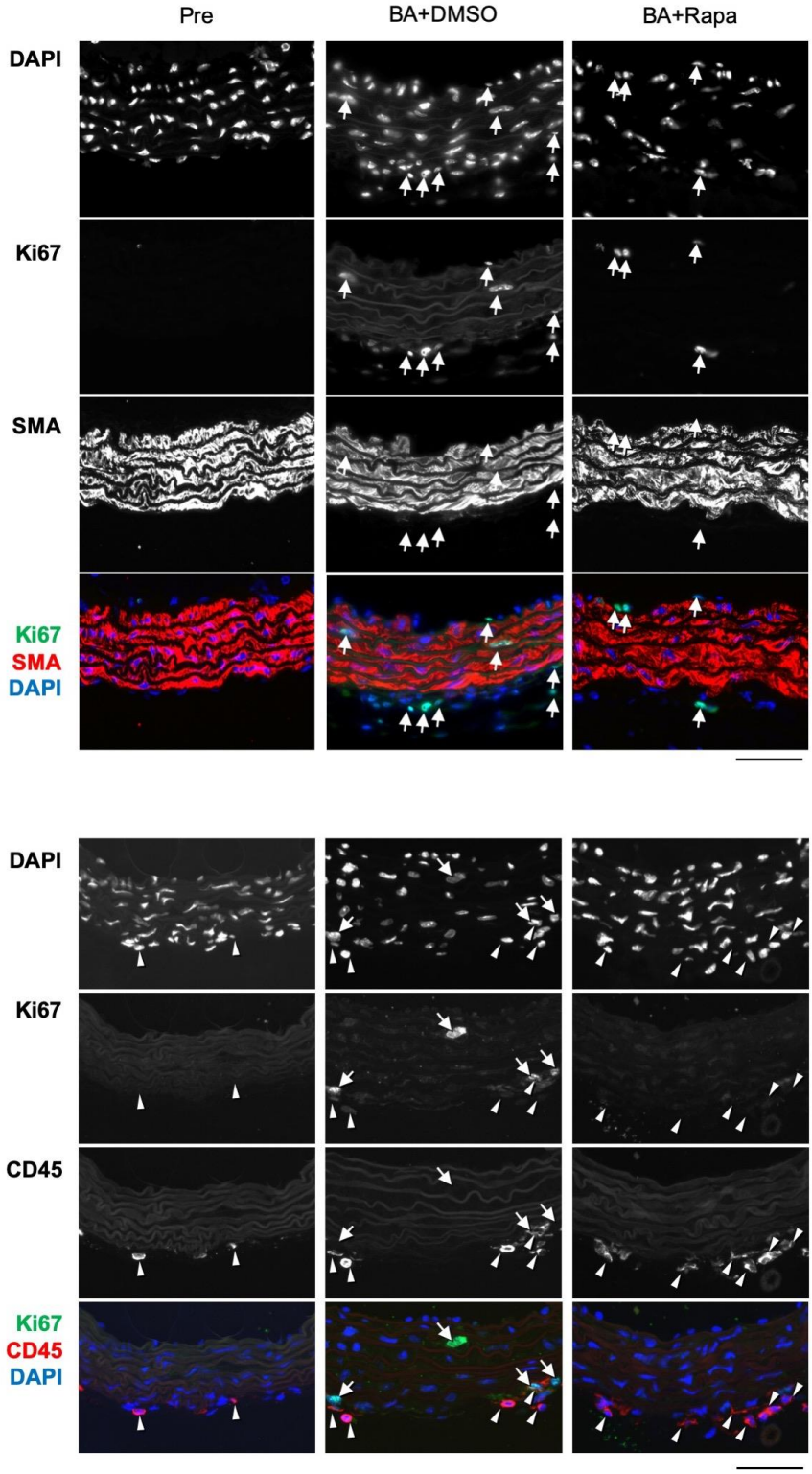


Supplemental Figure S1. Systolic blood pressure, pulse rate, and body weight before and after 14 days of BAPN+AngII challenge, with and without rapamycin treatment.

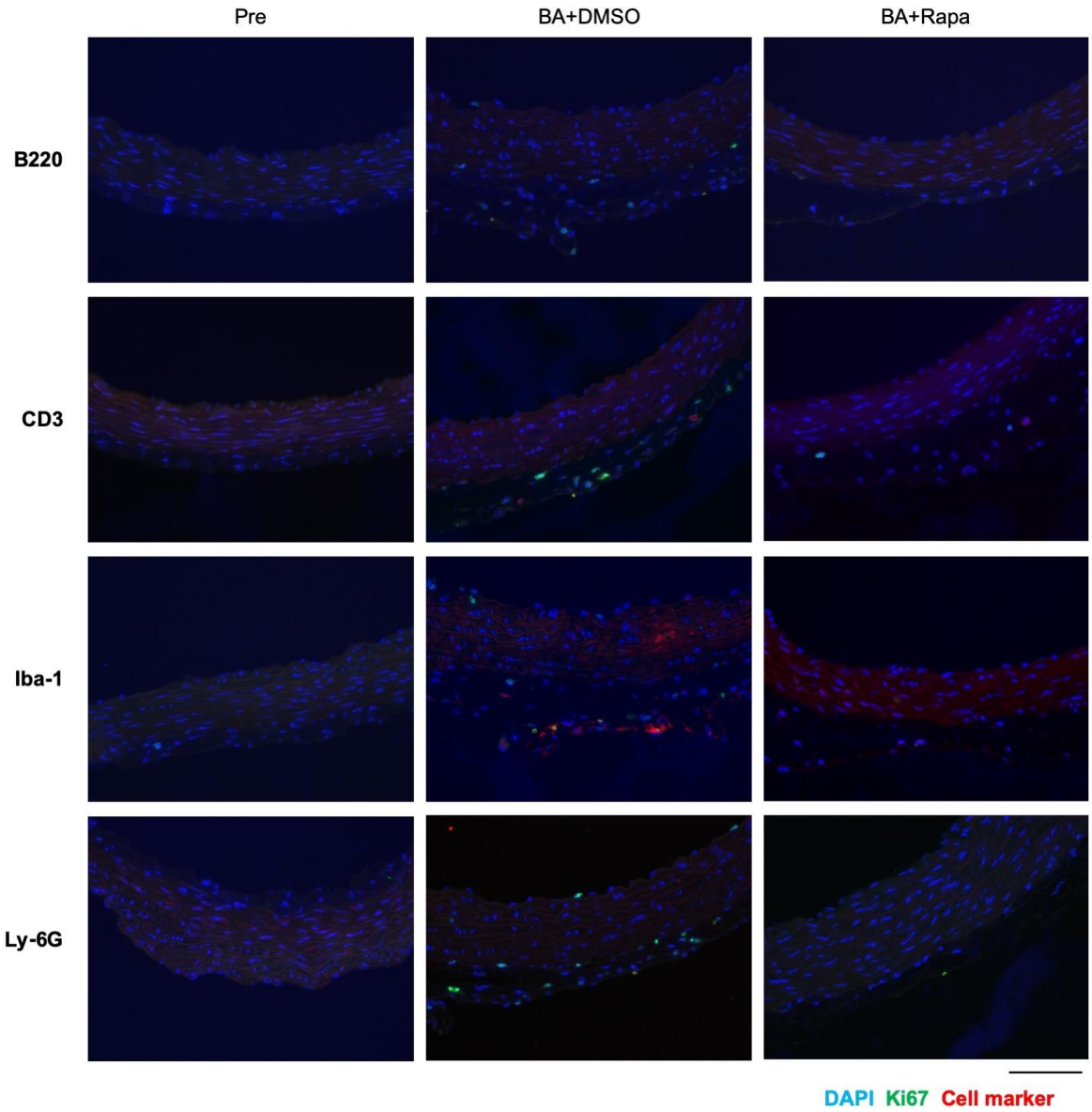


Supplemental Figure S2. Rapamycin treatment was performed either in the preventive intervention or in the therapeutic intervention. In the preventive intervention, intraperitoneal administration of rapamycin or vehicle (DMSO) was started on the day of the implantation of BAPN and AngII pumps, and continued throughout the 14-day observational period. In the therapeutic intervention, both the vehicle group and the rapamycin group received vehicle on the day of BAPN pump and AngII pump

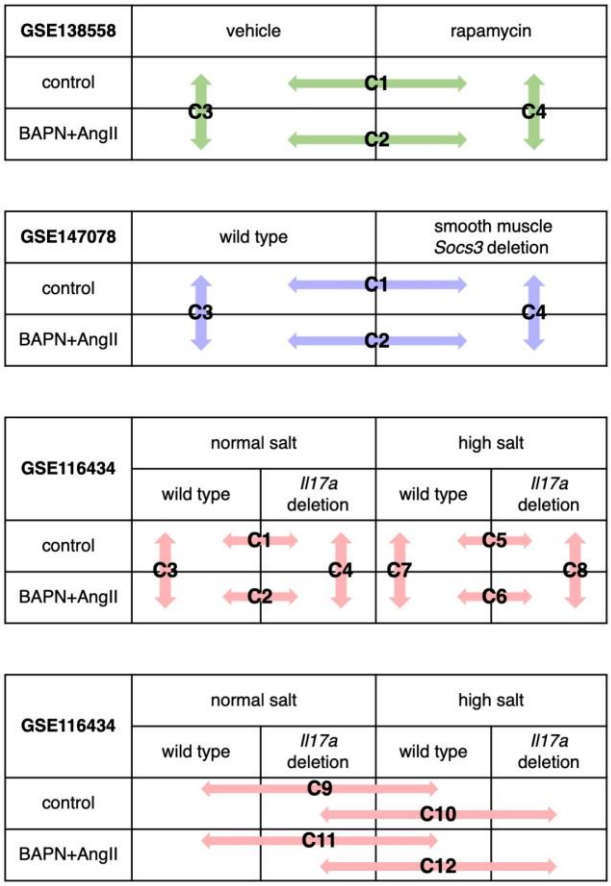
implantation and continued to day 7, when rapamycin administration was started, and continued for the rest of the observational period.



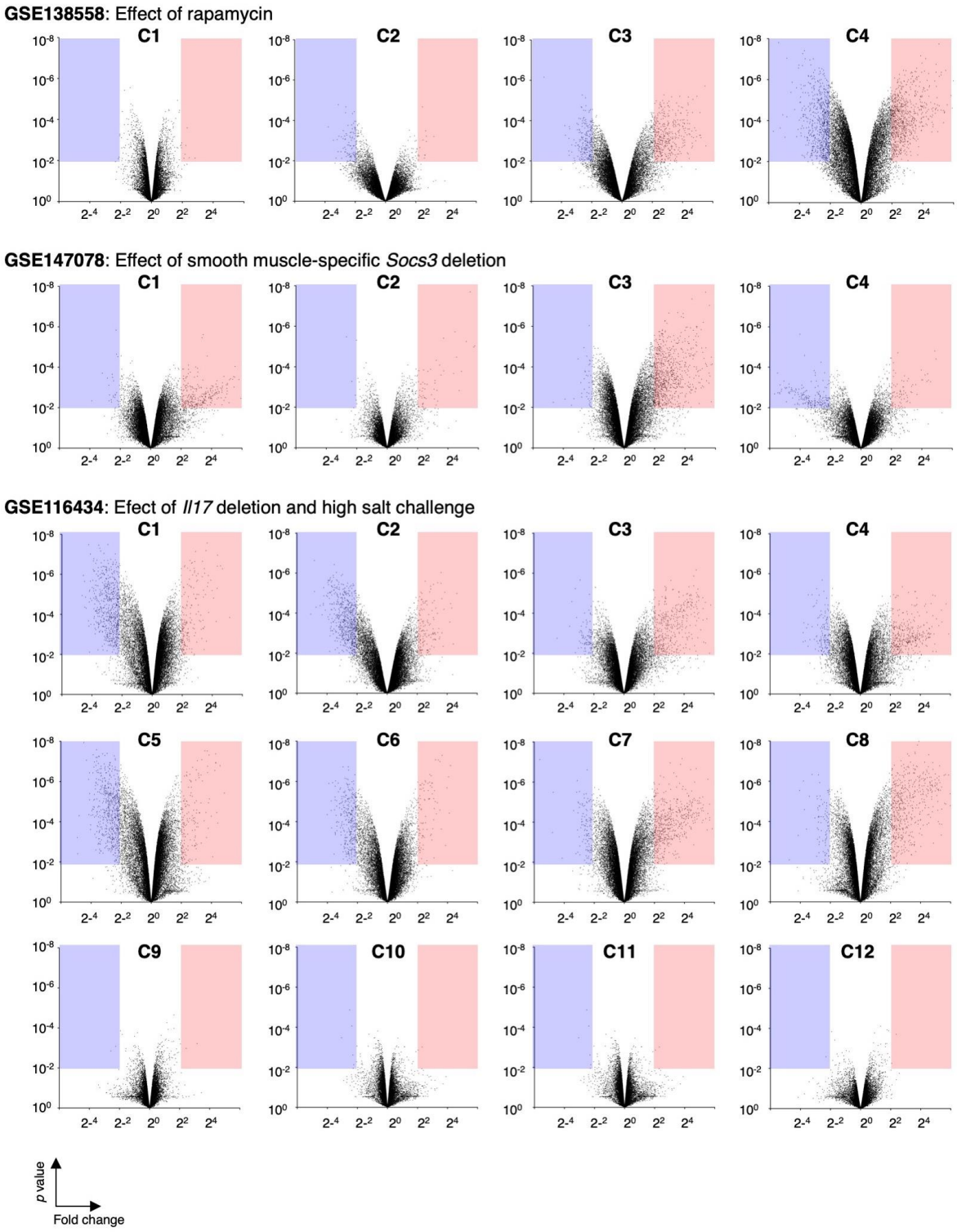
Supplemental Figure S3. Representative immunofluorescence staining images corresponding to Figure 2. Separate images for DAPI, Ki67, and SMA or CD45 stainings are shown in gray scale. Merged images are also shown in color. Arrows indicate Ki67-positive nuclei. Arrowheads indicate CD45-positive cells. Scale bars: 50 μm.



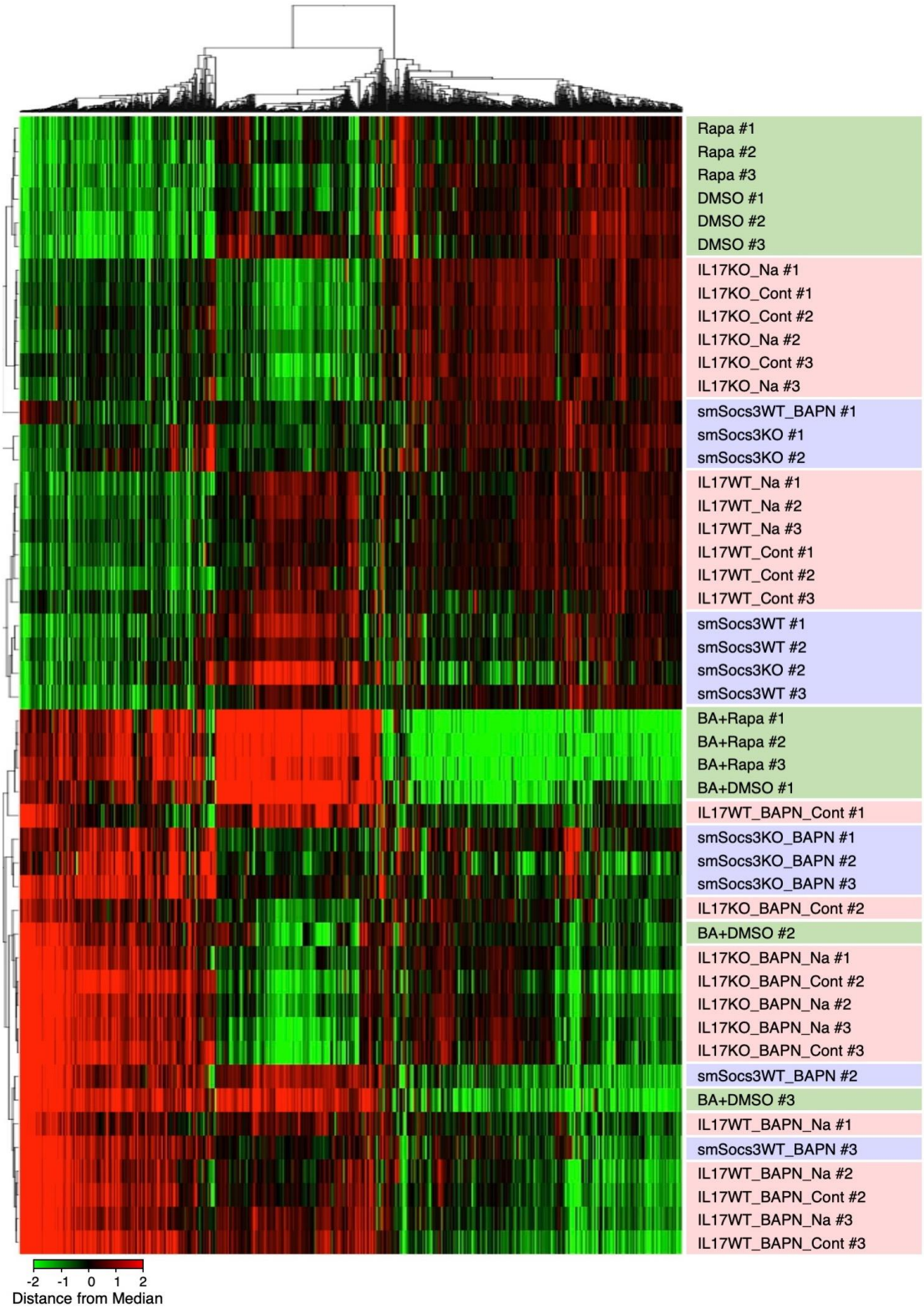
Supplemental Figure S4. Representative immunofluorescence staining images for Ki67 and cell type markers for B cells (B220), T cells (CD3), monocyte/macrophages (Iba-1), and neutrophils (Ly-6G). BAPN+AngII challenge was applied for 3 days with or without rapamycin treatment. Scale bar: 50 μm.



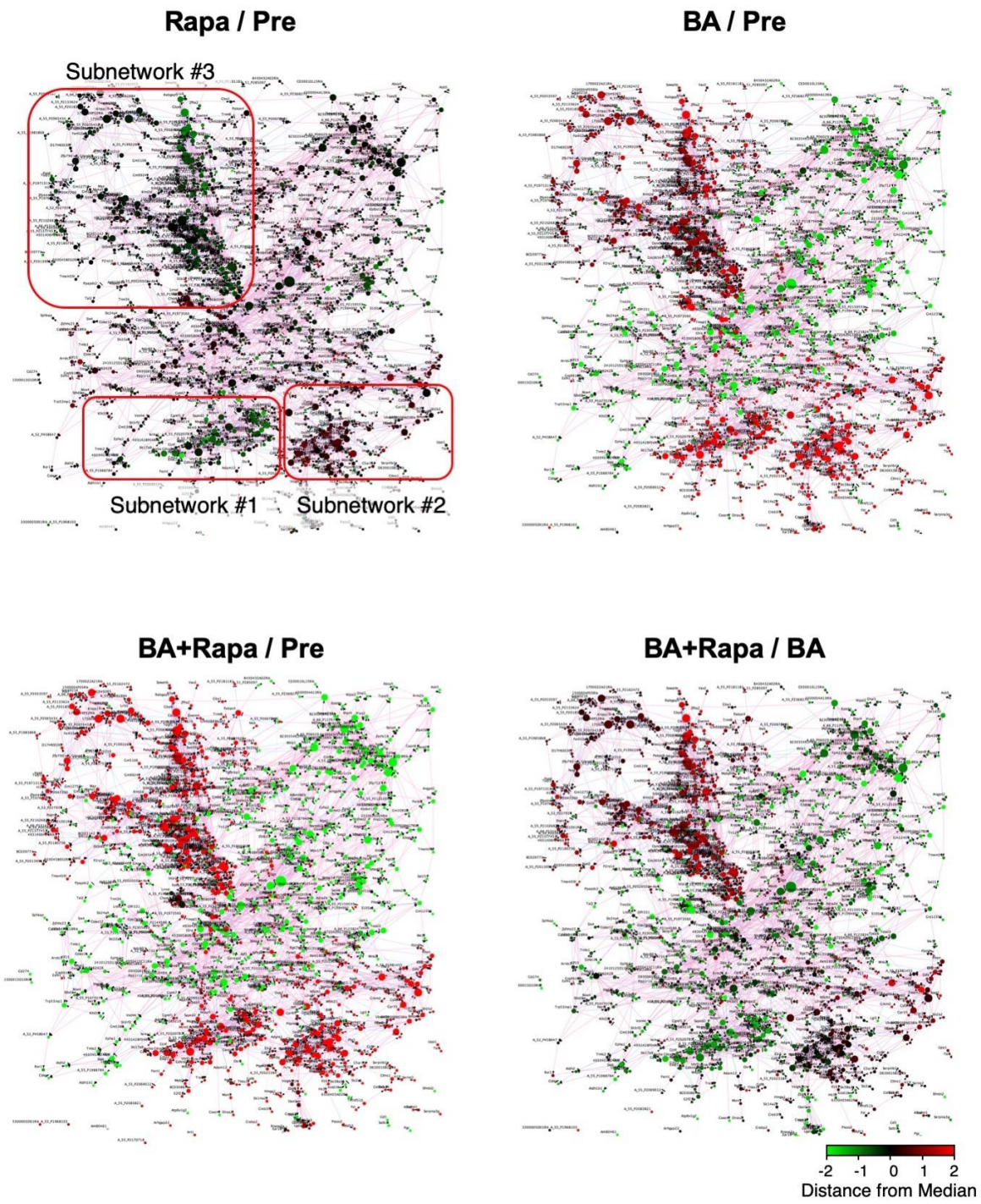
Supplemental Figure S5. The diagrams depict, by double arrows, the pair-wise comparisons in three transcriptome data sets; GSE116434 [21], GSE147078 [8], and GSE138558. All of the samples were thoracic aortas of the same AD model as the current study, with different experimental interventions. GSE116434: normal vs. high salt challenge and wild type vs. *Il17a* deletion. GSE147078: wild type vs. smooth muscle-specific *Socs3* deletion. GSE138484: vehicle vs. rapamycin. Each experimental group contained three biological replicates (mice), and in total 48 aortic samples were used to construct the gene expression network in the AD model. Twelve comparisons (C1–C12) for GSE116434, and 4 comparisons (C1–C4) each for GSE147078 and GSE138558 were made to extract the genes with significant changes in expression.



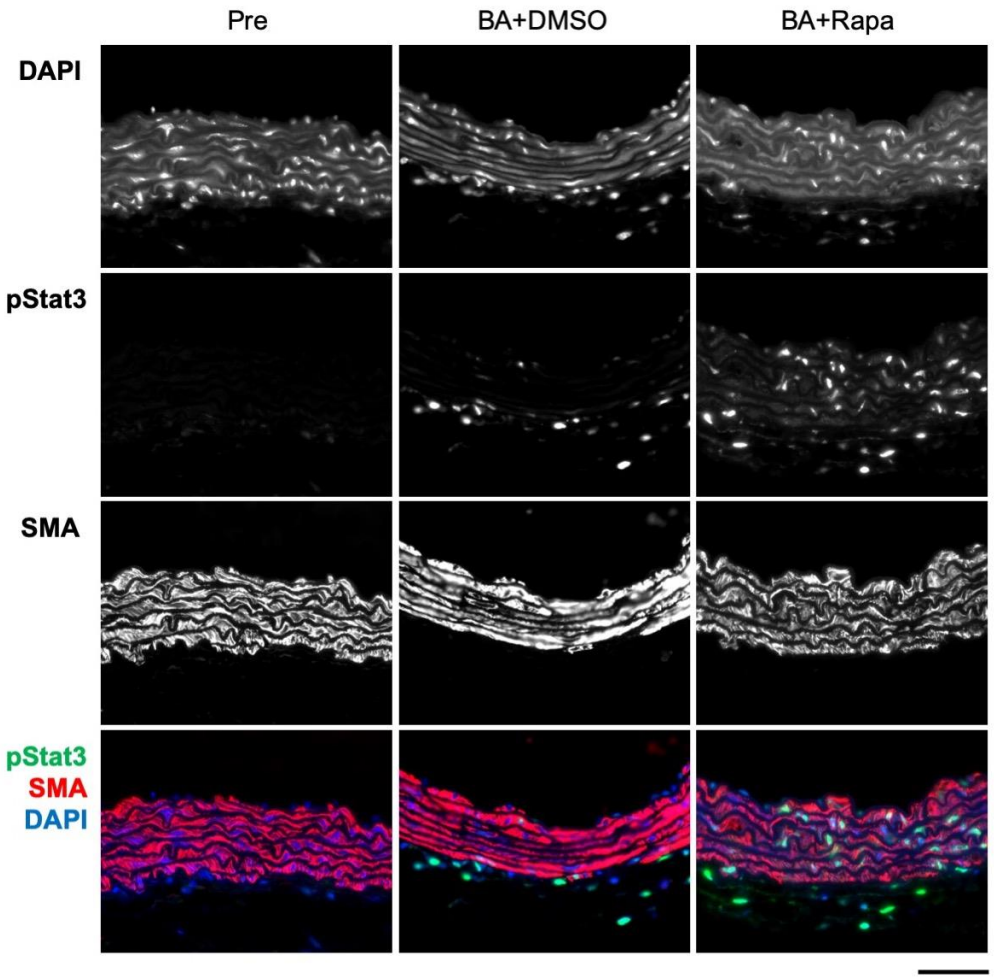
Supplemental Figure S6. Volcano plots for the comparisons in GSE116434 [21], GSE147078 [8], and GSE138558, as depicted in Supplemental Figure S3. The changes in gene expressions were considered significant when the fold changes were more than 4 (induced) or less than 0.25 (suppressed), and *p* values were less than 0.01. Induced genes and suppressed genes are indicated by red and blue shading, respectively.



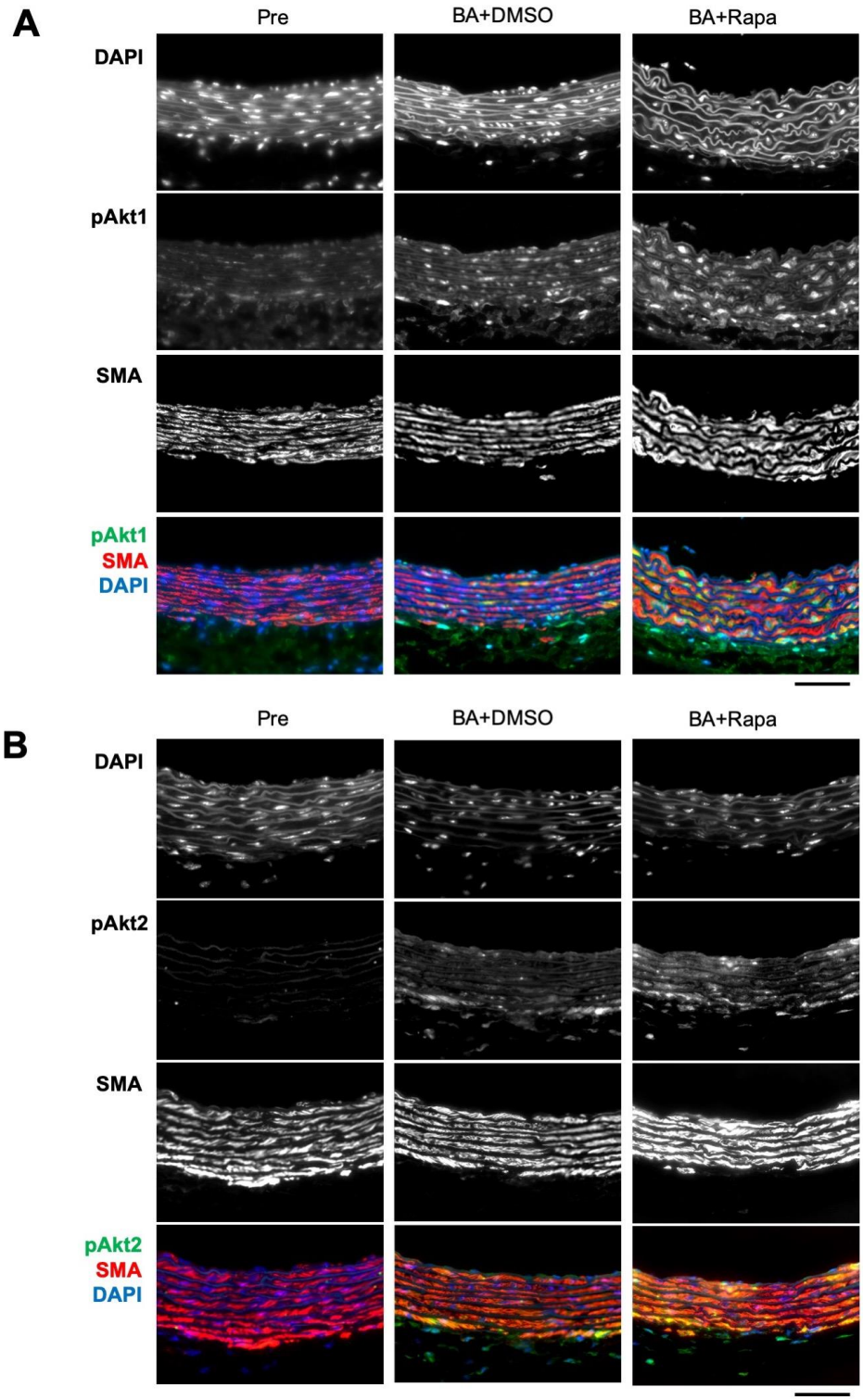
Supplemental Figure S7. The heat map representation of hierarchical clustering of the 1221 AD-related genes extracted from datasets GSE116434 [21], GSE147078 [8], and GSE138558. The sample names are color coded in red for GSE116434, blue for GSE147078, and green for GSE138558. These data were used for the gene network analysis in Figure 3.



Supplemental Figure S8. Gene expression network in AD. Organic plots of the gene expression according to Bayesian network analysis. Thoracic aortas were obtained with or without 3 days of BAPN+AngII challenge. The comparisons shown are between no intervention and rapamycin alone (Pre vs. Rapa), Pre and BAPN+AngII challenge (Pre vs. BA), Pre and BAPN+AngII challenge with rapamycin treatment (Pre vs. BA+Rapa), and BAPN+AngII challenge without and with rapamycin treatment (BA vs. BA+Rapa). Each node in the organic plots represents a single gene that is color coded for induction (red) or suppression (green) in a given comparison.



Supplemental Figure S9. Representative immunofluorescence staining images corresponding to pStat3 staining in Figure 5A. Separate images for DAPI, pStat3, and SMA staining are shown in gray scale. Merged images are also shown in pseudo color: blue, green, and red for DAPI, pStat3, and SMA, respectively. Scale bar: 50 μm.



Supplemental Figure S10. Representative immunofluorescence staining images corresponding to pAkt1 and pAkt2 staining in Figure 5A. Separate images for DAPI, pAkt1 or pAkt2, and SMA staining are shown in gray scale. Merged images are also shown in pseudo color: blue for DAPI, green for pAkt1 or pAkt2, and red for SMA. Scale bar: 50 μm.