Supplemental Material

Detailed Methods

General materials

Dulbecco's Modified Eagle Medium (DMEM) was from Gibco (Life Technologies, Carlsbad, CA). Recombinant mouse TNF-alpha was from R&D Systems (Minneapolis, MN). Z-VAD-FMK was from Bachem (Torrance, CA). Necrostatin-1 was from Sigma (St. Louis, MO). Primary antibodies used include anti-RIP3 (ProSci, Poway, CA), anti-RIP3 for human samples (Thermo Scientific, Rockford, IL), anti-RIP1 (BD Biosciences, San Jose, CA), anti-p65, anti-phospho-p65 (Ser536), anti-IκBα, anti-β-actin (Cell Signaling Technologies, Danvers, MA), anti-smooth muscle myosin heavy chain 11, anti-alpha smooth muscle Actin antibody, anti-alpha smooth muscle Actin antibody [1A4] (FITC), Rabbit IgG (Abcam, Cambridge, MA), anti-CD68 (AbD Serotec, Raleigh, NC), anti-phospho-p65 (Ser276), anti-PCNA, anti-PKCδ (Santa Cruz Biotechnology, Dallas, TX), Mouse IgG (Sigma, St. Louis, MO) and anti-NFκB antibody, p65 subunit, active subunit, clone 12H11 (Millipore, MA). Fluorophore-conjugated secondary antibodies and 4′6-diamidino-2-phenyl-indole, dihydrochloride (DAPI) were purchased from Molecular Probes (Life Technologies, Carlsbad, CA). Horseradish Peroxidase (HRP)-conjugated Antibodies were purchased from Bio-Rad (Hercules, CA). In Situ Cell Death Detection Kit was from Roche Applied Science (Indianapolis, IN). Elastin was stained by using Richard-Allan Scientific™ Elastic Stain kit (Thermo Scientific, Rockford, IL). The PKCδ siRNA (SI01388744) and its control siRNA (SI03650318) were purchased from Qiagen (Valencia, CA). The RIP3 siRNA (s80755) and its control siRNA (4390843) were *Silencer* Select siRNAs purchased from Ambion (Grand Island, NY). Lipofectamine RNAiMAX transfection reagent and Opti-MEM I medium were purchased from Invitrogen (Grand Island, NY). A nuclear extract kit was purchased from Active Motif (Carlsbad, CA). Other chemicals and reagents if not specified were purchased from Sigma-Aldrich (St. Louis, MO).

Mice

Rip3$^{+/-}$ mice[1] on a C57BL/6 background were generously provided by Dr. Vishva M. Dixit (Genentech, South San Francisco, CA). *Prkcd*$^{+/-}$ mice[2], generously providing by Dr Keiichi I. Nakayama of Kyushu University in Japan, were maintained on a mixed background of C57BL/6 and 129/Sv. Both mouse colonies were maintained by breeding heterozygous males and females. Litters were weaned at 3 weeks of age and genomic DNA isolated from tails was analyzed by PCR. PCR primers for *Rip3*$^{-/-}$ mice (5'-CGCTTTAGAAGCCTTCAGGTTGAC, 5'-GCAGGCTCTGGTGACAAGATTCATGG, and 5'-CCAGAGGCCACTTGTGTAGCG) produces a 700 bp band (wild-type *Rip3* allele) or a 450 bp band (*Rip3* deletion allele).[3] PCR primers for *Prckd*$^{-/-}$ mice (5'-CTGAAGGCTCTTTACTATTGCTTT, 5'-GCCCACAGCTTCTACTTTGTACCC, 5'-GGACCTCTGCACTCAGTGTTAGCA) produces a 900 bp band (wild-type *Prckd* allele) or a 650 bp band (*Prckd* deletion allele). C57BL/6J mice were purchased from The Jackson Laboratory (Bar Harbor, Maine). Male mice of 8~12 weeks old

were used for experiments. All animal experiments were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison (Protocol M02284).

Cell culture

Primary mouse aortic SMCs were isolated as described previously.[4, 5] Briefly, mouse aorta from the aortic arch to the iliac bifurcation was excised and incubated in digestion buffer (DMEM, Bovine serum albumin, Collagenase, Soybean trypsin inhibitor, and Elastase Type III) for 30 minutes at 37°C. Following removal of adventitia, arterial tissues was minced and further digested for 4 hours at 37°C. At the end of digestion, the mix was spun to a pellet by centrifugation and washed with 10% fetal bovine serum (FBS; Gemini, Woodland, CA) DMEM once, before suspension in a small volume of 10% FBS DMEM and left undisturbed for 48 hours to allow cells to migrate from tissue. Primary SMCs were grown at 37°C in 5% CO_2 in DMEM modified to contain 4mM L-Glutamine, 1g/L D-Glucose, and 110mg/L Sodium Pyruvate (Life Technologies, Carlsbad, CA) supplemented with 10% FBS, 100 U/mL penicillin, and 100 U/mL streptomycin. Cells between three and seven passages were used. The mouse aortic SMC cell line MOVAS cells and the mouse fibroblast cell line L929 cells were obtained from American Type Culture Collection (ATCC, Manassas, VA) and grown as recommended in DMEM modified containing 4.5g/L D-Glucose (Life Technologies, Carlsbad, CA) supplemented with 10% FBS, 100 U/mL penicillin, and 100 U/mL streptomycin.

Elastase-induced murine abdominal aortic aneurysm

Male mice aged 8-12 weeks underwent AAA induction by the elastase-perfusion model, as described previously.[6-8] After anesthesia, the mouse abdomen was shaved and scrubbed with povidone-iodine (Betadine). The mouse was then placed supine on the operative field. A long midline abdominal incision was made and the abdominal aorta, extending from where the left renal vein crosses the aorta to the iliac bifurcation, was isolated. The external diameter of the largest portion of abdominal aorta was measured with a digital caliber. All of the aortic branches between the renal arteries and bifurcation were ligated with 9-0 sutures. After placing temporary 6-0 silk ligatures around the proximal and distal aorta, an aortostomy was created with a 30G needle at the bifurcation. A heat-tapered segment of PE-10 polyethylene tubing (Baxter Healthcare Corp., Deerfield, IL) was introduced through the aortostomy and secured with a silk ligature. 0.45 U/mL type I porcine pancreatic elastase (Sigma, St. Louis, MO) was administrated to the infrarenal aorta through the tubing and allowed to incubate for 5 min at a constant pressure of 100 mm Hg. The 100mm Hg was calibrated using a saline bag hung at a height of 136cm. As a control, a separate group of mice were treated with equal concentration of heat-inactivated (100°C for 15 min) elastase for 5 min at a constant pressure of 100 mm Hg. The heat-tapered PE-10 polyethylene tubing was then removed and the aortotomy was closed with a 10-0 suture. The distal ligature was removed, followed by the removal of the proximal ligature. The abdominal incision was closed in two layers with 6-0 nylon sutures. Lidocaine 1% drops were placed on the wound. The mouse was kept on a warming pad until fully recovered from anesthesia. After the operation, mice were monitored each hour for the first 4 hours and then once daily. The external diameter of the largest portion of an abdominal aorta was measured and recorded at sacrifice, as it had been prior to elastase perfusion.

The percentage increase in maximal external aortic diameter was calculated. As shown in Figure 2A and Supplemental Figure 4, aortic perfusion with heat-inactivated elastase or elastase caused a 29.889%±4.644% (0.71mm±0.02mm) or 157.366%±9.973% (1.42mm±0.06mm) expansion in the wildtype mice, respectively. This is consistent with what is reported in the literature.[6]
Mice that underwent surgery were anesthetized using an isoflurane inhalant anesthetic: isoflurane was initially delivered via a chamber at 4%, followed by a mask at 2% isoflurane mixed with 100% oxygen. Mice were euthanized with 100% oxygen/5% isoflurane.

Orthotopic Allograft Transplantation

Orthotopic allograft transplantation of elastase-treated abdominal aorta was carried out as we reported recently.[9] The donor mouse was subjected to the elastase-perfusion procedure described above. Following the removal of perfusion catheter, the segment of elastase-treated aorta was transected between the upper ligation and aortostomy, and stored in saline containing heparin 100U/mL at 4ºC until transplantation. In the recipient mouse, after undergoing anesthesia and midline abdominal incision, the intestine was retracted to right side to expose the retro-peritoneum. The infrarenal aorta was dissected from the vena cava between the renal arteries to the iliac bifurcation. The branches of the abdominal aorta were exposed and ligated with 9-0 sutures. The donor aorta was end-to-side anastomosed to the recipient aorta with interrupted suture (11-0). After the distal anastomosis was completed, the distal ligature was removed, followed by the removal of the proximal ligature. The abdominal incision was closed in two layers with 6-0 nylon sutures. Lidocaine 1% drops were placed on the wound. The mouse was kept on a warming pad until fully recovered from anesthesia. Warm saline (0.5 mL) was subcutaneously injected to maintain fluid homeostasis. After the operation, mice were monitored each hour for the first 4 hours and then once daily. No antibiotics or immunosuppressants were used.

Adenoviral vectors and infection

Adenoviral vectors expressing PKCδ (AdPKCδ) and empty vector (AdNull) were constructed and purified by CsCl gradient centrifuging as previously described.[10, 11] The adenoviral vector expressing RIP3 were constructed and purified by Welgen, Inc (Worcester, MA). In vitro adenovirus infection was carried out as described previously.[11] Briefly, vascular SMCs ($1x10^5$ cells/well in 6-well plates) were incubated with adenovirus at indicated multiplicity of infection (MOI) in DMEM containing 2% FBS for 2 hours at 37°C. After removal of viral solutions, cells were cultured in DMEM containing 10% FBS for 24~48 hours.

RNA Isolation and Real-Time PCR (RT-PCR)

Total RNA was extracted from cultured cells or mouse aortic arteries using Trizol reagent (Life Technologies, Carlsbad, CA) according to manufacturer's protocols. Two microgram total RNA was used for the first-strand cDNA synthesis (Applied Biosystems, Carlsbad, CA). RT-PCR was carried out using the 7500 Fast Real-Time PCR System (Applied Biosystems, Carlsbad, CA). Each cDNA template was amplified in triplicate using SYBR Green PCR Master Mix (Applied

Biosystems, Carlsbad, CA) with gene specific primers. Primers for RT-PCR were QuantiTect Primers purchased from Qiagen (Valencia, CA). The relative mRNA levels were calculated using the $2^{-\Delta\Delta CT}$ method. GAPDH was used as the endogenous control.

Flow cytometric analysis

Cell death was evaluated by using an Annexin V-PE/7-AAD staining Kit (BD Biosciences, San Jose, CA). Cultures were rinsed with ice-cold PBS and incubated with accutase (Life Technologies, Carlsbad, CA) at 37°C for 2 min. The detached cells (from culture medium, PBS wash, and accutase treatment) were collected by centrifugation (2000 rpm, 5 min). Cell pellets were further washed twice with ice-cold PBS and resuspended in 100µl 1×binding buffer from the Annexin V-PE/7-AAD staining Kit. 5µl of PE Annexin-V and 5µl of 7-AAD were added to the cells and incubated at room temperature for 15 min. After incubation, 400µl binding buffer was added to each sample. Cells were analyzed using a Becton Dickinson Biosciences FACSCalibur (BD Biosciences, San Jose, CA).

In vivo Propidium Iodide (PI) staining

In vivo cell necrosis was examined by intraperitoneal (IP) injection of propidium iodide (PI).[12] Based on what was described by Trichonas et al.[12], PI (25 mg/kg body weight) was administered to mice through intraperitoneal (IP) injection. Two hours after PI administration, mice were euthanized and perfusion fixed with 4% formaldehyde. 6-µm-thick cryosections were cut. Mounting medium with DAPI was applied before fluorescence microscopy examination. Staining was immediately visualized with a Nikon Eclipse Ti inverted microscope system and digital images were acquired using a Nikon DS-Ri1 digital camera.

Immunoblotting

Cells were lysed in RAPI buffer (Sigma-Aldrich, St. Louis, MO) containing protease and phosphatase Inhibitors (Halt Cocktail, Thermo Scientific, Rockford, IL). Equal amounts of protein extract were loaded and separated by SDS-PAGE and then transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were blocked for 45min at room temperature with 5% skim milk in TBS plus 0.05% Tween 20, and then incubated with primary antibodies overnight at 4°C, followed by HRP-labeled secondary antibodies. Labeled proteins were visualized with an enhanced chemiluminescence system (PerkinElmer-cetus, Boston, MA) and ImageQuant LAS 4000 Mini (GE Healthcare Bio-Sciences, P.O. Pittsburgh, PA). For quantification, optical densities of proteins were determined by ImageJ (National Institute of Health, Bethesda, MD).

Immunohistochemistry

Tissues were perfusion-fixed with a mixture of 4% formaldehyde in phosphate buffered saline (PBS) and were imbedded in O.C.T. Compound (Sakura Tissue Tek, Netherlands) and sectioned to 6µm thickness using a Leica CM3050S cryostat. Tissue sections were permeabilized with 0.1% Triton X-100 in Tris-buffered saline (TBS) for 10 minutes at room temperature. Non-specific sites were blocked using 1% bovine serum albumin (BSA), 10% normal donkey serum in TBS for 2

hours at room temperature. Primary antibodies diluted in TBS with 1% BSA were then applied onto arterial sections, and incubated overnight at 4°C. On the second day, arterial sections were rinsed with TBS plus 0.025% Triton X-100, followed by incubating with fluorophore-conjugated secondary antibodies diluted in TBS with 1% BSA for 1 hour at room temperature. DAPI was used to stain the nuclei. Staining was visualized with a Nikon Eclipse Ti inverted microscope system and digital images were acquired using a Nikon DS-Ri1 digital camera. To quantify the immunofluorescence intensity, fluorescent images of each set of experiments were acquired under the same microscope exposure settings to allow comparative quantification. We used ImageJ software to quantify the fluorescence intensity of cells and background fluorescence for each image. The following formula was used to calculate the corrected fluorescence. Corrected fluorescence= Integrated Density- (Area of a Region of Interest (ROI)×Mean fluorescence of background).

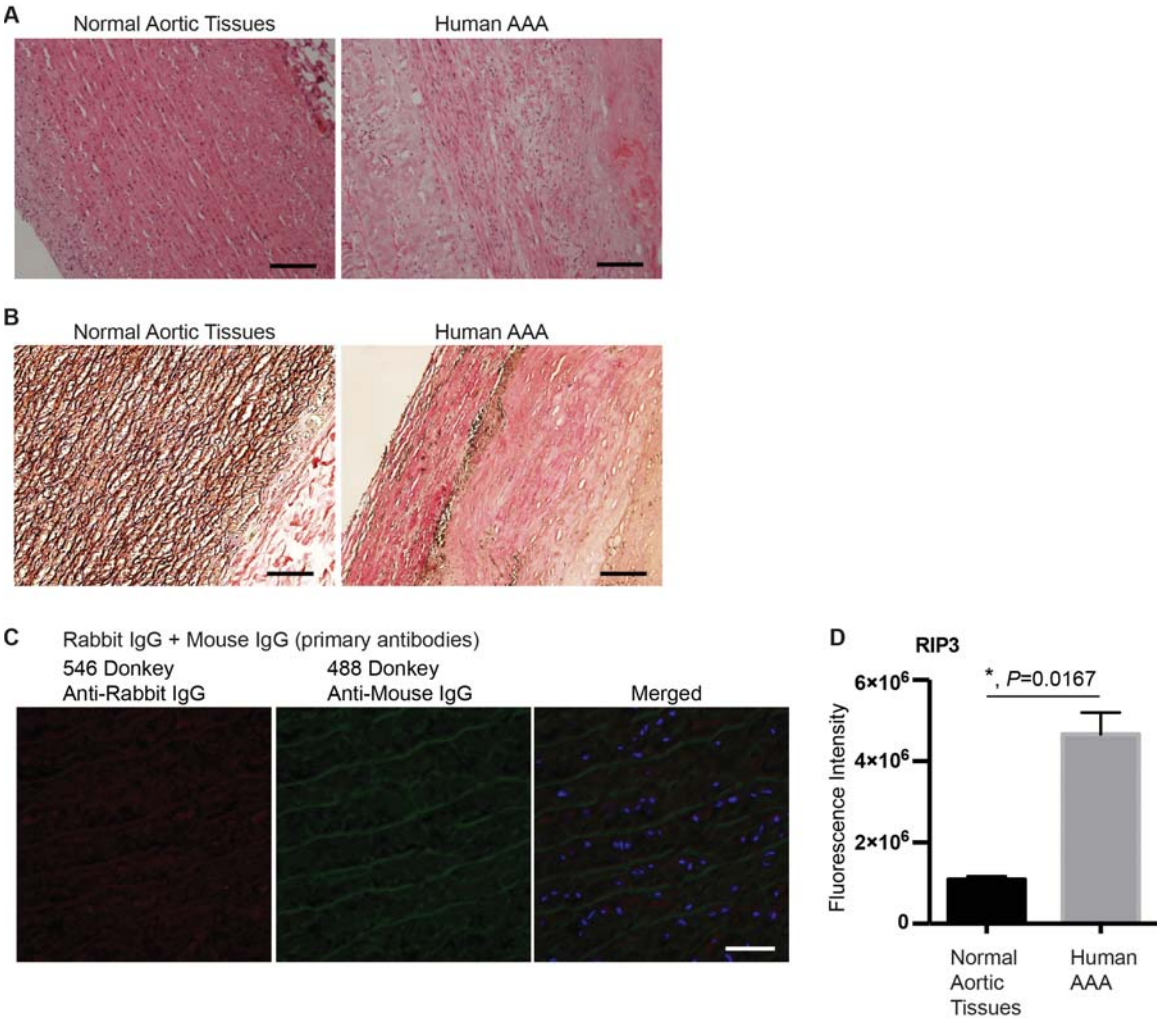
Statistical analysis

Data are presented as mean±SEM. Two-tailed Student's *t*-test for normally distributed data and Mann-Whitney nonparametric test for skewed data that deviate from normality were used to compare two conditions. One-way ANOVA with Bonferroni's post-hoc test for normally distributed data and Kruskal-Wallis nonparametric test for skewed data were used to compare three or more means. Differences with $P<0.05$ were considered statistically significant.

Study approval

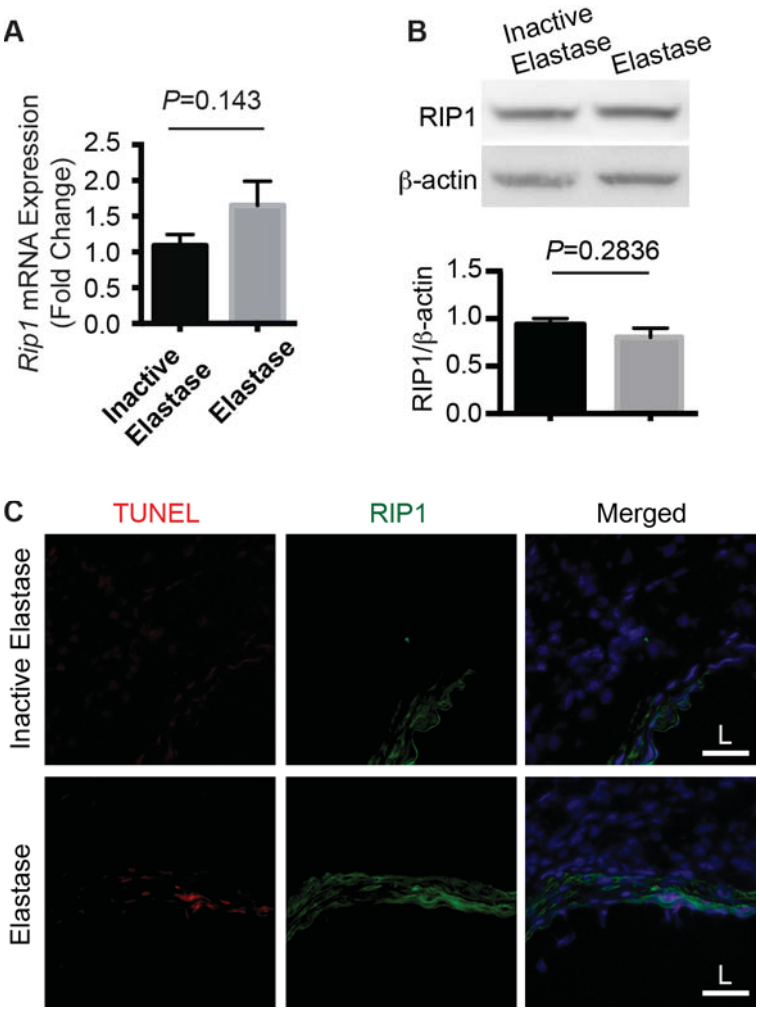
Human study protocol was approved by the institutional Review Board of Zhejiang University, China (H2012036). The studies were conducted according to Declaration of Helsinki principles. All animal experiments were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison (Protocol M02284) and performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the United States National Institutes of Health.

Online Figures



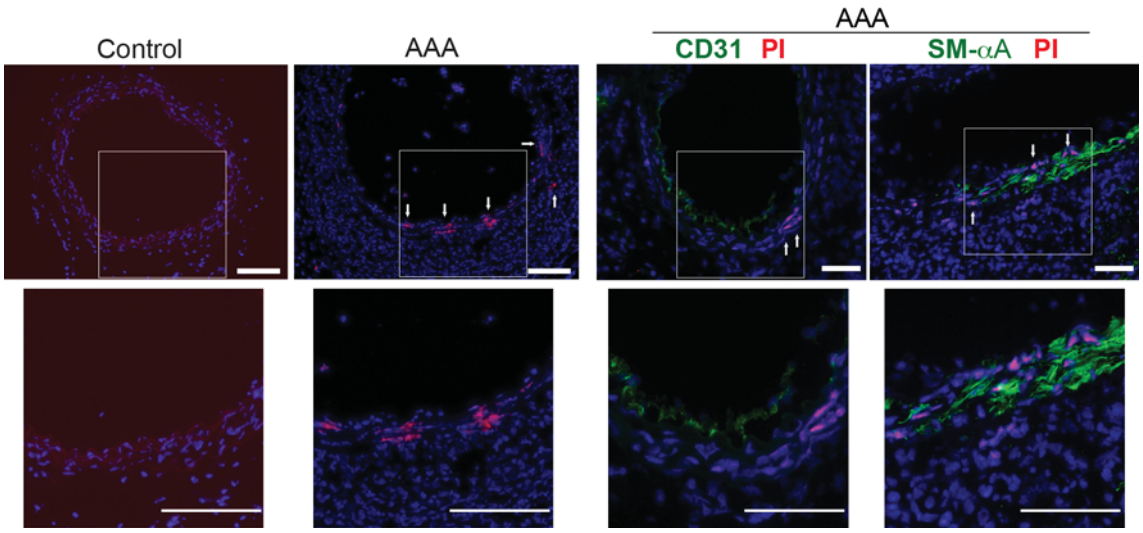
Online Figure I.

Analysis of human aneurysmal and normal aortic tissues. (**A**) Representative images of H&E staining of cross-sections from human aneurysmal and normal aortic tissues. Scale bars=200μm. (**B**) Human aneurysmal and normal aortic cross-sections were stained for Verhoeff-Van Gieson (VVG). Scale bars=200μm. (**C**) Representative images of immunohistochemistry controls. Human aortic cross-sections were incubated with indicated IgG antibodies followed by incubation with indicated secondary antibodies. Scale bar=50μm. (**D**) Fluorescence intensity analysis of RIP3 expression in human normal and aneurysmal aortic cross-sections. Data are mean±SEM. n=4.



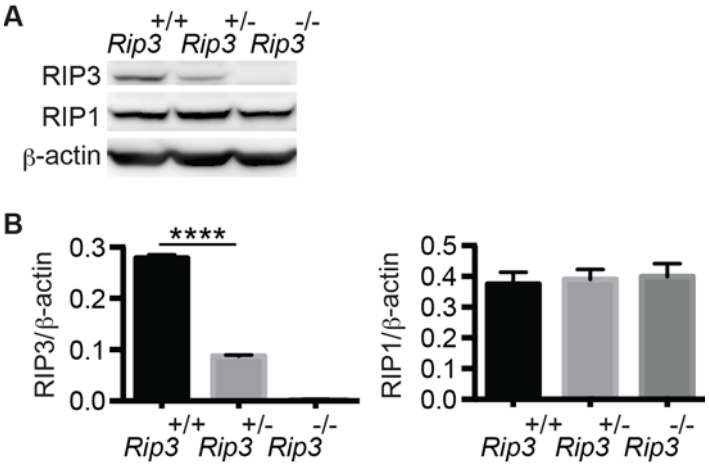
Online Figure II

Analysis of RIP1 expression in elastase-induced mouse AAAs. (**A**) Real-time PCR and (**B**) Western blotting analyses of RIP1 mRNA and protein expression, respectively, in C57BL/6 mouse arteries perfused with elastase or heat-inactivated elastase on Day 14 post-perfusion. Data are mean±SEM. n=8(A), n=4(B). (**C**) Representative images of aortic cross-sections harvested from C57BL/6 mice on Day 3 post-perfusion with elastase or inactive elastase. Sections were co-stained for RIP1 and TUNEL. L indicates lumen. n=3. Scale bars=50μm.



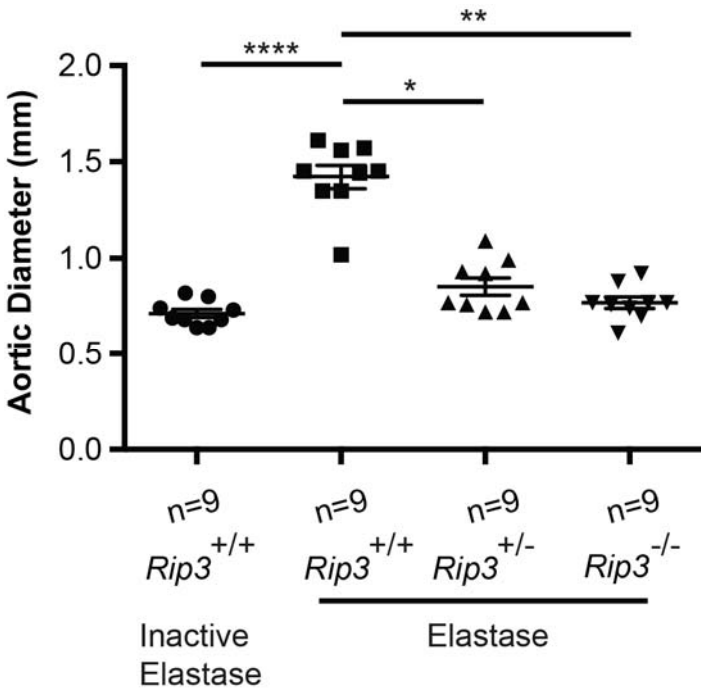
Online Figure III.

Increased cell necrosis in abdominal aortic aneurysm tissues. Representative photographs of aortic cross sections of normal or elastase-perfused aortae (Day 7 post-perfusion). Propidium iodide (PI) was administered to mice via intraperitoneal injection 2 hours prior to sacrifice. Following PI staining, aortic sections were also stained for CD31 or SM-αA. Higher magnified views of highlighted regions were shown at the bottom. L indicates lumen. Scale bars=100μm.



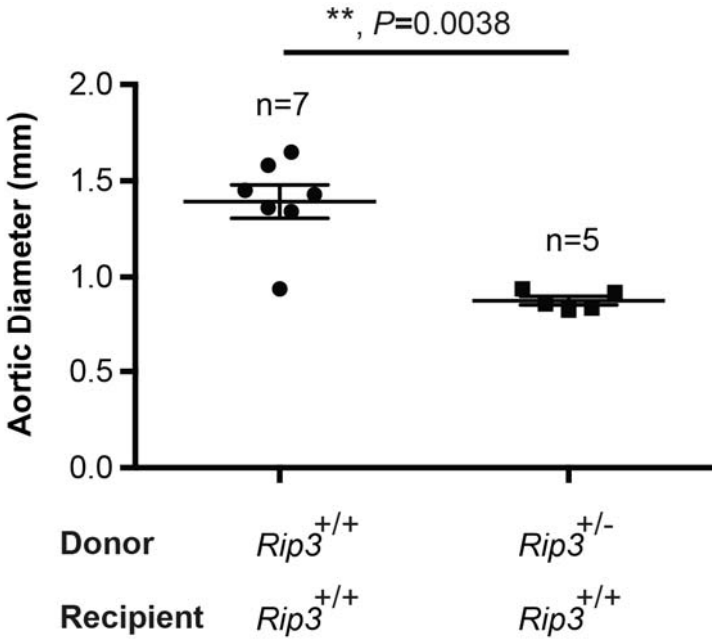
Online Figure IV

RIP1 and RIP3 protein levels in *Rip3*$^{+/+}$, *Rip3*$^{+/-}$ and *Rip3*$^{-/-}$ arteries. (**A**) Representative Western blots and (**B**) quantifications of RIP1 and RIP3 protein in aortic tissues harvested from *Rip3*$^{+/+}$, *Rip3*$^{+/-}$ and *Rip3*$^{-/-}$ mice. RIP1 protein levels were not affected by *Rip*3 gene deletion. Data are mean±SEM. n=3.



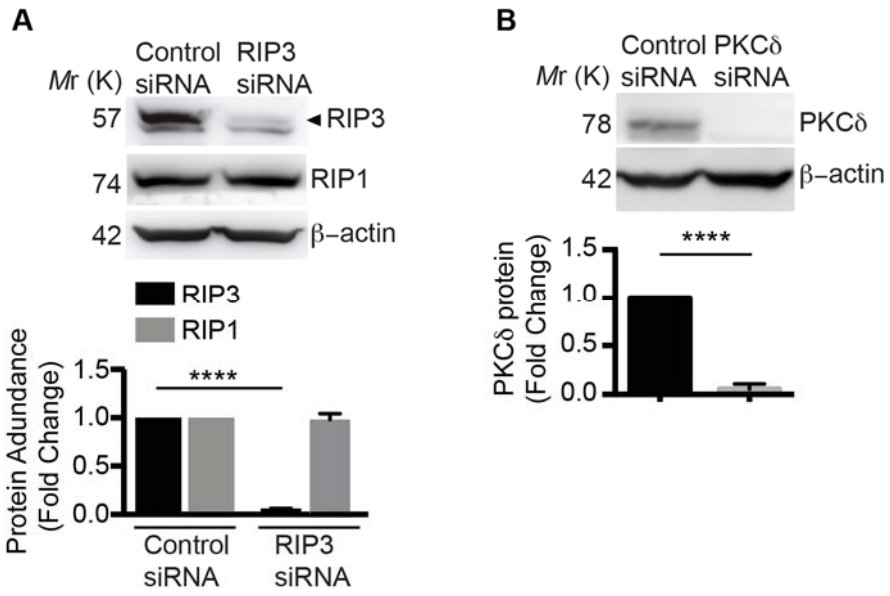
Online Figure V

***Rip3* deficiency protects mice from developing abdominal aortic aneurysm.** Aortic diameters measured 14 days after elastase perfusion. **P*<0.05; ***P*<0.005; *****P*<0.0001.



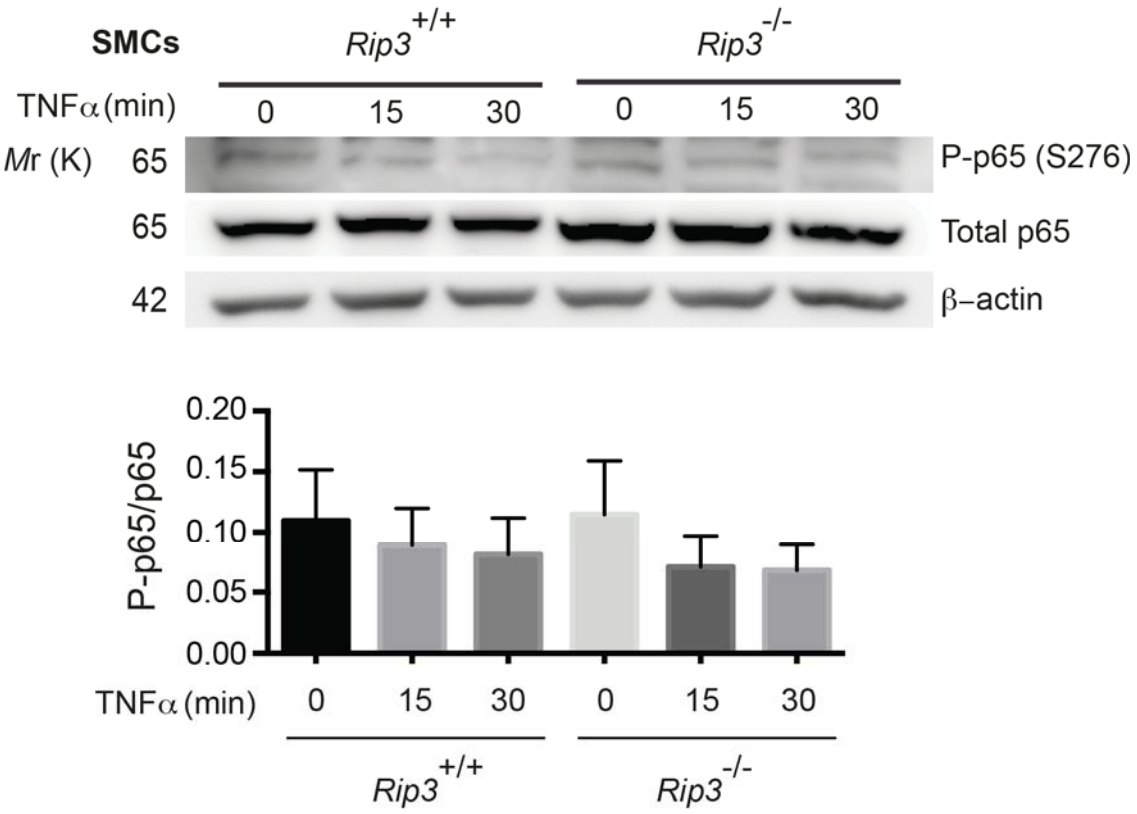
Online Figure VI

Rip3 **in the vascular wall is necessary for abdominal aortic aneurysm formation**. Donor aortic diameters measured 14 days after elastase perfusion and transplantation.



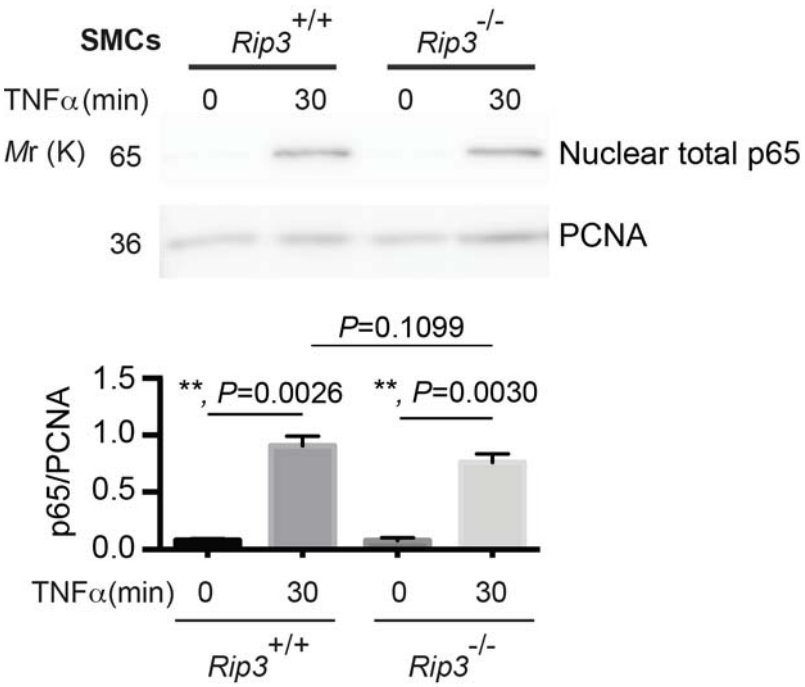
Online Figure VII

Quantifications of RIP3 and PKCδ knockdown. Cell lysates were collected 36 hours post-transfection and aliquots of 40μg were subjected to Western blot analysis of RIP3 (**A**); PKCδ (**B**). Data are mean±SEM. n=3 (A) and 6 (B). ****P<0.0001.



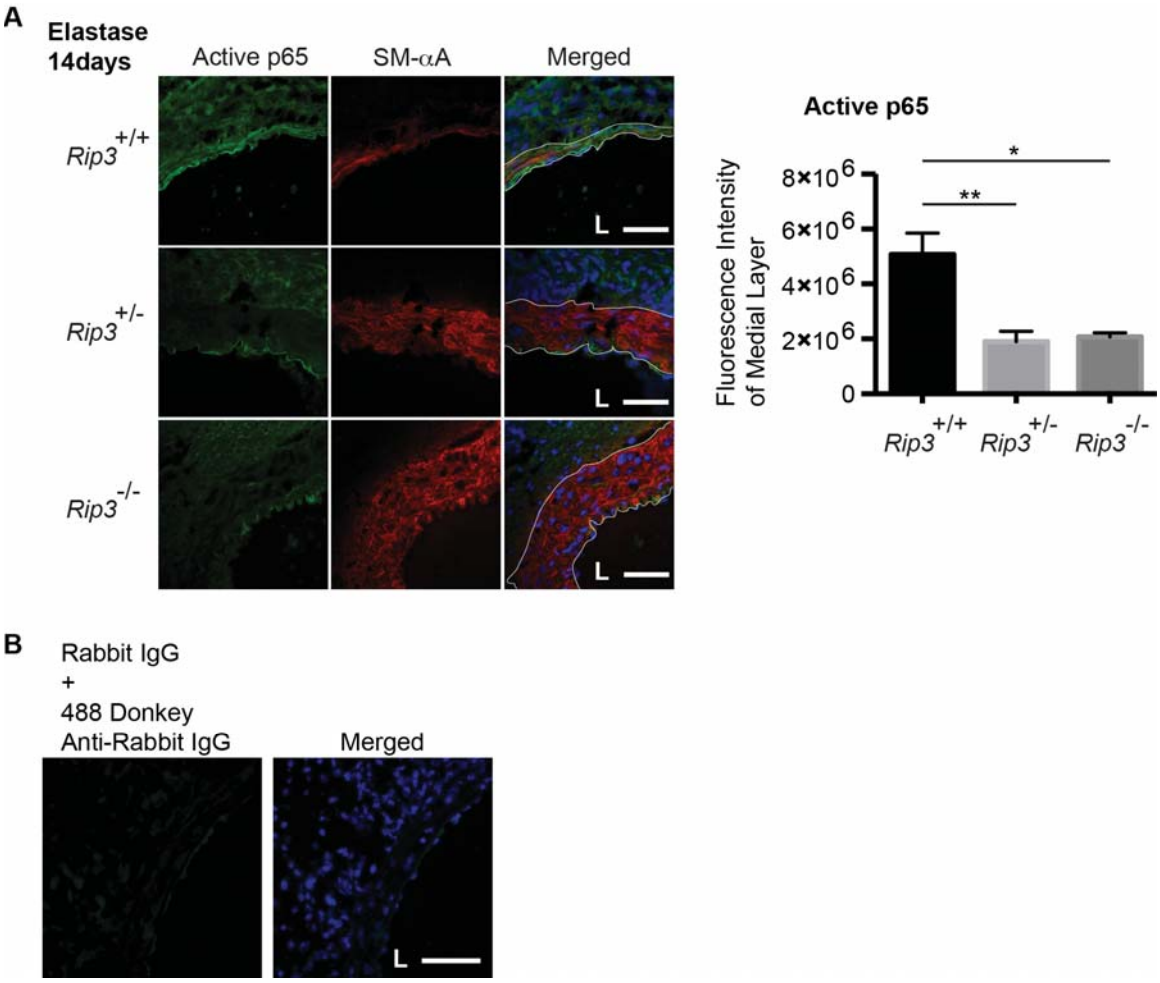
Online Figure VIII

Phosphorylation of p65 on serine 276 is not significantly changed in *Rip3*$^{+/+}$ or *Rip3*$^{-/-}$ SMCs following TNFα treatment. Aortic SMCs isolated from *Rip3*$^{+/+}$ and *Rip3*$^{-/-}$ mice were treated with 10ng/ml TNFα for indicated time. Cell lysates were subjected to Western blot analysis with indicated antibodies. Data are mean±SEM. n=3.



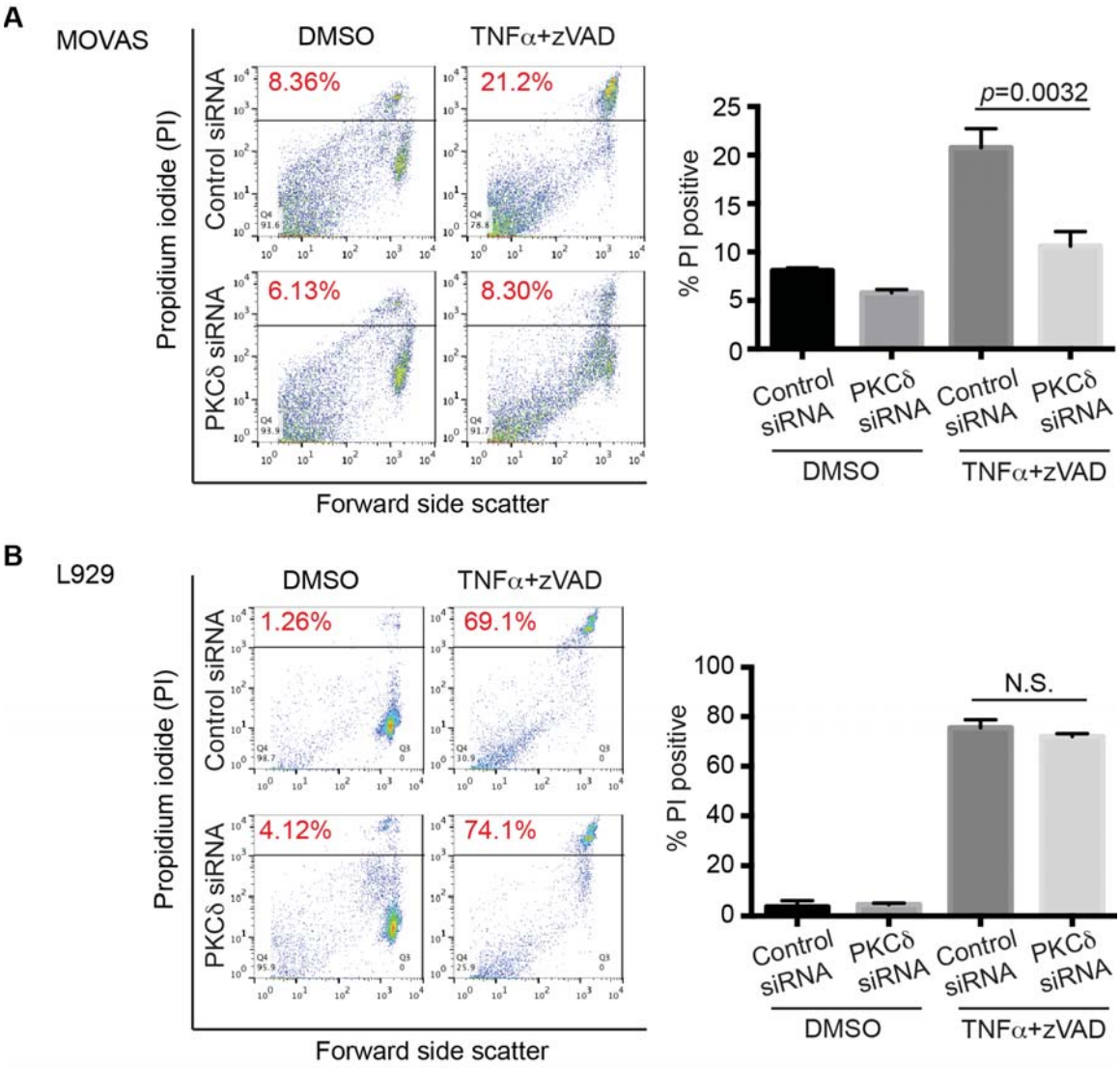
Online Figure IX

***Rip3* deletion does not affect TNFα induced nuclear retention of p65 in SMCs.** Aortic SMCs isolated from *Rip3*$^{+/+}$ and *Rip3*$^{-/-}$ mice were treated with PBS or 10ng/ml TNFα for 30min. Nuclear proteins were isolated and subjected to Western blot analysis with indicated antibodies. Data are mean±SEM. n=4.



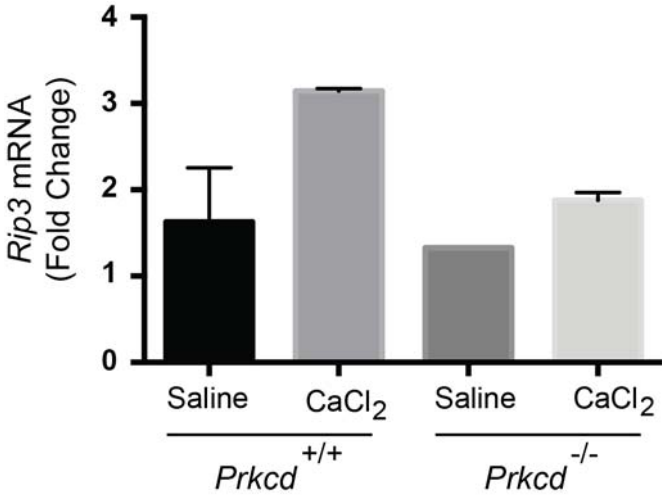
Online Figure X

Rip3 **deficiency significantly reduced NFκB activation in medial layer of aortae perfused with Elastase. (A) Left panel:** Representative images of aortic cross-sections harvested from mice on Day 14 post-perfusion with elastase. Sections were co-stained for active p65 and SMc-αA. L indicates lumen. Scale bars=25μm. **Right panel:** Analysis of fluorescence intensity (active p65) in the medial layer (indicated by white line). Data are mean±SEM. n=4~6. **P*<0.05, ***P*<0.005. (**B**) Representative images of an immunohistochemistry control. Aortic cross-sections were incubated with a Rabbit IgG antibody followed by incubation with indicated secondary antibodies. Scale bar=50μm.



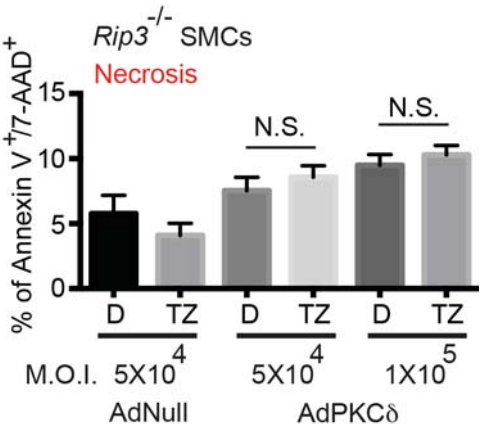
Online Figure XI

Transient knockdown of PKCδ protects MOVAS cells but not L929 cells from TNFα induced necroptosis. (**A**) MOVAS cells or (**B**) L929 cells were transfected with 10nM control siRNA or PKCδ-specific siRNA for 24 hours followed by treatment with DMSO (vehicle control) or 20ng/ml TNFα plus 20μM zVAD (an established *in vitro* necroptosis induction protocol) for additional 24 hours (**A**, MOVAS) or 16 hours (**B**, L929). Cells were accutased and incubated with 5μg/ml of propidium iodide (PI) at 37 °C for 10 min. Cell necrosis (PI-positive cells) was determined by flow cytometric analysis. Data represent mean±SEM. n=3.



Online Figure XII

***Rip3* mRNA upregulation in $CaCl_2$ treated arteries (7 days) is diminished in *Prkcd*$^{-/-}$ mice.** Real-time PCR analyses of *Rip3* mRNA levels in *Prkcd*$^{+/+}$ and *Prkcd*$^{-/-}$ arteries 7 days after saline or $CaCl_2$ treatment. Data are mean±SEM. n=2.



Online Figure XIII

Overexpressing PKCδ does not rescue the necroptosis defect of *Rip3*$^{-/-}$ SMCs. *Rip3*$^{-/-}$ aortic SMCs were infected with AdNull or AdPKCδ at indicated M.O.I. 48 hours post-infection, cells were treated with DMSO (D, vehicle control) or TNFα plus zVAD (TZ) for 24 hours. Cell necrosis was determined by flow cytometric analysis following PE Annexin V and 7-AAD staining. Necrotic cells were identified as PE Annexin-V^{+}/7-AAD^{+}. Data represent mean±SEM. n=4 (E). N.S.=not significant.

Supplemental References

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