Supplementary tables

Animal models and pathogenesis of thoracic aortic aneurysm

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**Table S1**. Recent studies employing BAPN-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species, strain | Sex | Age  (w) | BAPN  dose | Induction  time, w | Aortic diameter Increase | TAA  Rate, % | Rupt.  rate,% | Dissection | Ref |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | NR | Yes | [1] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | NR | Yes | [2] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 45.7 | Yes | [3] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | 73.3 | 46.7 | Yes | [4] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | <80 | Yes | [5] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | NR | NR | 80 | Yes | [6] |
| Mice, C57BL/6 | M | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 23.3 | Yes | [7] |
| Mice, C57BL/6 | NR | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | 14.3 | Yes | [8] |
| Mice, C57BL/6 | NR | 3 | 1 g/kg/d in DW | 4 w | Yes | NR | >50 | Yes | [9] |
| Mice, C57BL/10 | M | 3 | 0.5 g/kg/d in DW | 4 w | NR | NR | <60 | Yes | [10] |
| Mice, C57BL/6 | M | 3 | 0.5 g/kg/d in DW | 4 w | Yes | NR | 11 | Yes | [11] |
| Mice, C57BL/6 | M | 3 | 0.5 g/kg/d in DW | 4 w | NR | NR | 12.5 | Yes | [12] |
| Mice, C57BL/6 | M & F | 3 | 0.5 g/kg/d in DW | 1, 2, 3 or 4 w | Yes | NR | 86.7 (M)  58.8 (F) | Yes | [13] |
| Mice, C57BL/6 | M | 3 | 0.4 g/100 g diet | 18 d | Yes | NR | NR | Yes | [14] |
| Mice, C57BL/6 | M | 3 | 6 g/L in DW | 4 w | Yes) | 83.3 | NR | Yes | [15] |
| Mice, C57BL/6 | NR | 3 | 2.5g/L in DW | 4 w | Yes | 42.9 | 42.9 | Yes | [16] |
| Mice, C57BL/6 SJL | M | 3-4 | 3 g/L in DW | 26 w | Yes | 50 | 15.2 | NR | [17] |
| Mice, C57BL/6 | M | 3 | 1 g/L in DW | 6 w | Yes | NR | 66 | NR | [18] |
| Rats, SD | M | 3 | 1 g/kg/d, intragastric | 4 w | Yes | 16.7 | 0 | NR | [19] |

BAPN, β-aminopropionitrile; d, day; DR, drink water; F, female; M, male; NR, not reported; Rupt., rupture; SD, Sprague-Dawley; w, weeks.

**Tablel S2.** Recent studies employing rodent TAA models induced by angiotensin II infusion

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Strain | Sex | Age,  W | Dose,  μg/kg per min | Time, W | TAA rate, % | Rupture rate, % | Dissection  rate, % | Ref |
| Mice | ApoE−/− | M | 12 | 1 | 4 | NR | NR | NR | [20] |
| Mice | ApoE−/− | M | 8-10 | 1 | 4 | NR | NR | NR | [21] |
| Mice | ApoE−/− | M | adult | NR | NR | NR | NR | NR | [22] |
| Mice | Wild type  and  Plce1−/− | M&F | 10 to 12 | 1 | 4 | 80% | 43% | NR | [23] |
| Mice | Wild type  and  Loxl4−/− | M | 14 or 20 | 1 or 1.5 | 4 | 28.6% | NR | NR | [24] |
| Mice | Wild type and  Tfam−/− | M | 4-5 | 1 | 4 | 100% | 70% | 70% | [25] |
| Rat | SD | F | 8 | 1.2 | 4 | 85% | NR | NR | [26] |

ApoE−/−, apolipoprotein E-deficient; F, female; Loxl4−/−, lysyl oxidase (LOX)-like proteins 4-deficient; M, male;NR, not reported; Plce1−/−, phospholipase Cε-insufficient; SD, Sprague-Dawley; Tfam−/−, mitochondrial transcription factor A-deficient;W, week.

**Table S3**: Recent studies employing elastase-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species,  strain | Sex | Age, w | PPE site | PPE dose | PPE time,  min | Experimental period, w | TAA rate, % | Rupture rate, % | Dissection rate, % | Ref |
| Mice,  C57BL/6 | M | 8-12 | ATA & arch | 15 µL | 5 or  10 | 1-4 | 43 or  71 | 0 or 18 | NR | [27] |
| Mice,  C57BL/6 | M | 8-12 | DTA | NR | 4 | 2 | NR | NR | NR | [28] |
| Mice,  C57BL/6 | M | 8-10 | DTA | 12 μL | 3 | 2 | 100 | NR | NR | [29] |
| Rats, SD | F | 12 | DTA | NR | 15-20 | NR | NR | NR | NR | [30] |

ATA, ascending thoracic aorta; DTA, descending thoracic aorta; NR, not reported; PPE, porcine pancreatic elastase; SD, Sprague-Dawley; TAA, thoracic aortic aneurysm; w, week.

**Table S4**. Recent studies employing CaCl2-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species, strain | Sex | Age | CaCl2  Conc. | CaCl2  time, min | Exp. Duration,  Weeks | Aortic diameter increase | TAA  Rate, % | Rupt.  rate,% | Dissection rate, %  (or yes/no) | Ref |
| Mice,  129/SvE | M&F | NR | 0.5 M | 15 | 4 | 25% | NR | NR | NR | [31] |
| Mice,  C57BL/6 | M&F | 10 w | 0.5 M | 15 | 4, 8, 16 | 59.5% 4 w  64.3% 8 w  62.9% 16 w | 90% | NR | NR | [32] |
| Rats, WS | M | NR | 0.5 M | 15 | 4 | 18% | NR | NR | NR | [33] |
| Rats, SD | NR | NR | 0.5 M | 15 | 4 | NR | NR | NR | NR | [34] |

CalCl2, calcium chloride; Conc., concentration; Exp., experimental; F, female; M, male; NR, not reported; Ref, reference; Rupt., rupture; SD, Sprague-Dawley; TAA, thoracic aortic aneurysm; w, week; WS, Wistar.

**Table S5.** Recent studies employing combination of BAPN and angiotensin II-induced TAA models in rodents

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Species | Strain | Sex | Age,  W | BAPN | | | Angiotensin II | | TAA rate, % | TAA diameter increase | Rupture | Dissection | Reference |
|  |  |  |  | Dose | Time, days | Route | Dose,  μg/kg/min | Time, day |  |  |  |  |  |
| Mice | C57BL/6 | M | 3 | 0.15 μg/kg/d | 28 | i.p. | 1 | 3 | 40 | Yes | Yes | NR | [35] |
|  |  |  |  |  |  |  |  | 28 | 73 |  |  |  |  |
| Mice | C57BL/6 | M & F | 10–15 | 0.2% | 28 | DW | 1 | 25 (3 days after initiation of BAPN) | NR | Yes | Yes | NR | [36] |
| Mice | C57BL/6, or FVB | M | 3 | 0.4% | 28 | Diet | 1 | 1 | NR | NR | Yes | Yes,100% | [37] |
| Mice | C57BL/6 | M | 3 | 1 μg/kg/d | 28 | DR | 1 | 2 | 25 | Yes | Yes | Yes | [38] |

BAPN, β-aminopropionitrile; DR, drinking water; i.p., intraperitoneal;NR, not reported; TAA, thoracic aortic aneurysm; W, week;

**Table S6: Recent studies investigating potent therapeutic target against TAA in animal models**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TAA induction | Animals | Intervention | TAA incidence | Aortic diameter | Rupture | Mechanism | Targets | Ref |
| Inflammation | | | | | | | | |
| BAPN | C57BL/6 mice | Dexamethasone | ↓ | ↓ | NR | ↓ Macrophage and neutrophil infiltration  ↓ Apoptosis of VSMC  ↓ MMP 2/9  ↓ ECM degradation | Inflammation  Apoptosis  ECM degradation | [3] |
| Genetic | VSMC-specific Tgfbr2- deficient mice | Dexamethasone | ↓ | ↓ | NR | ↓ CCL8  ↓ Macrophage infiltration  ↓ MMP2  ↓ NF-*κ*B | Inflammation | [39] |
| Genetic | Fbn1C1039G/+ mice | Folic acid | ↓ | ↓ | NR | ↓ NOX4  ↓ Superoxide production  ↓ Elastin fiber fragmentation | Inflammation  ECM degradation | [40] |
| BAPN | C57BL/6 | Metformin | ↔ | ↓ | ↔ | ↓ Inflammation  ↓ Elastin breakage | Inflammation  ECM degradation | [15] |
| BAPN | C57BL/6 mice | Melatonin | ↓ | ↓ | ↓ | ↑ SIRT1 signalling  ↓ Macrophage infiltration  ↓ MMP2, MMP9  ↓ Reactive oxygen species  ↓ VSMC loss | Inflammation  Oxidative stress | [7] |
| Genetic | Fbn1mgR/mgR | Digoxin | NR | ↓ | NR | ↑ miR-122,  ↓ CCL2  ↓ MMP12  ↓ Elastin fragmentation | Inflammation  ECM degradation | [41] |
| BAPN | C57BL/6 | Oltipraz (Nrf activator) | ↓ | ↓ | ↓ | ↓ Apoptosis  ↓ Macrophage infiltration  ↓ MMP | Inflammation  Apoptosis | [9] |
| BAPN | C57BL/6 mice | TEPP-46 (activator of glycolytic enzyme pyruvate kinase M2) | ↓ | ↓ | ↓ | ↓ Inflammatory cells infiltration  ↓ ROS  ↓ Caspase 1  ↓ VSMCs loss | Inflammation  Oxidative stress  Apoptosis | [8] |
| CaCl2 | Sprague-Dawley rats | Cordycepin, (an anti-inflammatory and antioxidant compound) | ↓ | ↓ | NR | ↓ VEGF  ↓ IL-6, TNF-α and IL-1β  ↓ ROS  ↓ Caspase 3/9 and apoptosis | Inflammation  Oxidative stress  Apoptosis | [34] |
| BAPN | C57Bl/6 mice | Myriocin | ↓ | NR | ↓ | ↓ Inflammation (IL-1β, TNF-  α, and IL-6) | Inflammation | [12] |
| BAPN+  AngII | C57Bl/6 mice | Senkyunolide I | ↓ | ↓ | ↓ | ↓ Inflammation  ↓ ROS  ↓ Apoptosis  ↑ Elastin integrity | Inflammation  Oxidative stress  Apoptosis  ECM degradation | [42] |
| Ang II,  BAPN,  Genetic | Mice | Allopurinol | ↓ | ↓ | ↓ | ↓ Uric acid  ↓ Inflammation | Inflammation | [43] |
| Ang II | ApoE−/− mice | Angiotensin 1-7 | ↓ | ↓ | NR | ↓ Inflammation  ↓ MMP2, 9  ↑ Elastin integrity | Inflammation | [21] |
| BAPN | C57BL/10 mice | Macrophage inhibitors Ki20227, mLR12 | ↓ | ↓ | ↓ | ↓ Macrophage infiltration  ↓ Inflammation  ↓ MMP 2&9 | Inflammation | [10] |
| BAPN  TAC  Genetic | C57B/L6 mice  Fbn1C1041G/+ mice | Angiogenic factor with G-patch and FHA domains 1 | ↓ | ↓ | NR | ↓TGF-β and ERK1/2  ↓ Inflammation | TGFβ  Inflammation | [16] |
| BAPN | C57/BL6 SJL | Moderate aerobic exercise | ↓ | ↓ | ↓ | ↓ TGF-β pathway  ↓ Inflammatory markers  ↑ Elastogenesis | Inflammation  ECM formation | [17] |
| Genetic | Fbn1C1039G/+ mice | Antisense oligonucleotide against angiotensinogen | ↓ | ↓ | NA | ↓ Inflammatory gene expression  ↓ Elastin fragmentation | Inflammation  ECM degradation | [44] |
| Elastase | C57Bl/6 mice | Administration of mesenchymal stem cells | ↓ | ↓ | NR | ↓ T cell, neutrophil and macrophage infiltration  ↓ Proinflammatory cytokines  ↑ Anti-inflammatory IL-10  ↓ Elastic degradation | Inflammation  ECM degradation | [28] |
| Apoptosis | | | | | | | | |
| BAPN | SD rats | Methamphetamine | ↑ | ↑ | ↑ | ↑ MMP 2&9  ↑ Elastin breakage  ↑ VSMC apoptosis | Apoptosis  ECM degradation | [19] |
| BAPN | C57BL/6 Mice | Ciprofloxacin (antibiotic) | ↑ | ↑ | ↑ | ↑ Apoptosis  ↑ MMP9  ↑ ECM degradation | Apoptosis  ECM degradation | [2] |
| BAPN | C57BL6 mice | Diesel exhaust particulate | ↑ | ↑ | ↔ | ↑ apoptosis  ↑ BAX/Bcl2  ↑ Caspase 3/cleaved Cas3 | Apoptosis | [45] |
| BAPN | C57BL/6 mice | Dexamethasone | ↓ | ↓ | NR | ↓ Macrophage and neutrophil infiltration  ↓ Apoptosis of VSMC  ↓ MMP 2/9  ↓ ECM degradation | Inflammation  Apoptosis  ECM degradation | [3] |
| BAPN | C57BL/6 mice | TEPP-46 (activator of glycolytic enzyme pyruvate kinase M2) | ↓ | ↓ | ↓ | ↓ Inflammatory cells infiltration  ↓ ROS  ↓ Caspase 1  ↓ VSMCs loss | Inflammation  Oxidative stress  Apoptosis | [8] |
| CaCl2 | SD rats | Cordycepin, (an anti-inflammatory and antioxidant compound) | ↓ | ↓ | NR | ↓ VEGF  ↓ IL-6, TNF-α and IL-1β  ↓ ROS  ↓ Caspase 3/9 and apoptosis | Inflammation  Oxidative stress  Apoptosis | [34] |
| Genetic | Fbn1C1041G/+ mice | Nitro-oleic acid | ↓ | ↓ | NR | ↓ ERK1/2  ↓ Smad2  ↑ NF-κB  ↓ MMP2  ↓ Apoptosis | TGFβ  Inflammation  Apoptosis | [46] |
| BAPN | C57BL/6 | Oltipraz (Nrf activator) | ↓ | ↓ | ↓ | ↓ Apoptosis  ↓ Macrophage infiltration  ↓ MMP | Inflammation  Apoptosis | [9] |
| ECM degradation | | | | | | | | |
| Genetic | Fbn1C1039G/+ mice | Rapamycin | ↓ | ↓ | NR | ↓miR-126-3p and subsequent ERK1/2 signalling  ↓MMP-9 expression  ↓Elastin degradation | ECM degradation | [47] |
| BAPN | C57BL/6 mice | Rapamycin | ↓ | ↓ | ↔ | ↓ mTOR pathway  ↓ Macrophage and neutrophil infiltration  ↓ MMP9  ↓ Elastic fiber fragmentation | mTOR  ECM degradation | [4] |
| Genetic | Mice deficient in hamartin, an inhibitor of mTOR | Rapamycin | ↓ | NR | NR | ↓ mTOR activation  ↓ Elastic fiber fragmentation | mTOR  ECM degradation | [48] |
| Genetic | Fbln4SMKO C57BL/6 mice | Dabigatran (thrombin inhibitor)  Rivaroxaban (factor Xa inhibitor) | ↓ | NR | NR | ↓ Protease activated receptor 1 | ECM | [49] |
| Genetic | Fbn1C1039G/+ mice | ODQ (sGC inhibitor)  KT5823 (PRKG inhibitor)  PRKG1 silencing | NR | ↓ | NR | ↓Elastin fiber fragmentation | NO–sGC–PRKG  ECM degradation | [50] |
| Genetic | Fbn1mgR/mgR mice | DAPT (Notch inhibitor) | NR | ↓ | ↓ | ↓ Elastin degradation | ECM degradation | [51] |
| Genetic | Fbn1C1039G/+ mice | HIPK2 Inhibitor BT173 | ↓ | ↓ | ↓ | ↓ Elastin fiber fragmentation  ↓Collagen accumulation | ECM degradation | [52] |
| Genetic | Fbn1C1039G/+ mice | Flutamide (androgen receptor blocker) | NR | ↓ | NR | ↓ Erk1/2, Smad2  ↓ MMP2  ↓ Elastin fiber fragmentation | TGFβ  ECM degradation | [53] |
| BAPN | C57BL/6 mice | Crocin (MMP inhibitor) | ↓ | ↓ | ↓ | ↓ MMP activity  ↓ Elastin degradation | ECM degradation | [5] |
| Genetic | Fbn1C1039G/+ mice | Nicotinamide riboside (NAD+ precursor to normalize mitochondrial function) | NR | ↓ | NR | ↑ Mitochondrial dysfunction  ↓ Elastin fiber fragmentation | Mitochondrial function  ECM degradation | [25] |
| Ang II | SD rats | AgomiR-22 | NR | ↓ | NR | ↓ MMP-9  ↑ ECM integrity | ECM degradation | [26] |
| CaCl2 | C57BL/6 mice | miR-133a overexpression | ↓ | ↓ | NR | ↓ Pro – protein convertase furin  ↓ Elastic fiber fragmentation | ECM degradation | [32] |
| Miscellaneous | | | | | | | | |
| Genetic | Fbn1C1039G/+ mice | Vitamin B | ↓ | ↓ | NR | ↑Smad4  ↑ collagen maturation | Collagen maturation | [54] |
| Genetic | Fbn1mgR/mgR mice | baclofen (GABAB receptor agonist) | ↓ | ↓ | ↓ | ↑ muscle contractility  ↑ aortic wall microarchitecture | Contractility | [55] |
| TGFβ inhibition | Zebrafish | TGFβ antagonist LY364947 | ↑ | ↑ | NR | ↓ pSmad3 | TGFβ | [56] |

↔, no effect; ↑, increase; ↓, decrease; Ang II, angiotensin II; ApoE−/−, apolipoprotein E-deficient; BAPN, β-aminopropionitrile; Bcl2, B-cell lymphoma 2; CaCl2, calcium chloride; CCL, chemokine (C-C motif) ligand; ECM, extracellular matrix; Erk, extracellular signal–regulated kinase; Fbn1, fibrillin-1; Fbln4, fibulin-4; Fbln4SMKO, smooth muscle-specific fibulin-4 knockout; GABA, gamma-aminobutyric acid; HIPK2, homeodomain-interacting protein kinase 2; IL, interleukin; MMP, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NF-κB, Nuclear Factor Kappa B;NO, nitirc oxide; NR, not reported; Nrf: nuclear factor erythroid 2-related factor 2; Ltbp, latent TGFβ-binding protein; NOX4, NADPH oxidase 4;PRKG1, type 1 cGMP-dependent protein kinase; Ref, reference; ROS, reactive oxygen species; SD, Sprague-Dawley; sGC, soluble guanylate cyclase; SIRT1, sirtuin 1; Smad, suppressor of mothers against decapentaplegic; TGFβ, transforming growth factor-beta; Tgfbr2, TGFβ type 2receptor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VSMCs, vascular smooth muscle cells.

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