Data input form: MouseAGE Database

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Preferred acknowledgement: **Cardiovascular disease**

Summarise supporting data attached:

Ageing / disease: ABDOMINAL AORTIC ANEURYSM

Model: APOE KNOCKOUT MICE INFUSED WITH ANGIOTENSIN II FOR 28 DAYS.

Clinically relevant? (Yes or No): YES

Explanation of why clinically relevant or not:

Abdominal aortic aneurysm (AAA) is a localized dilatation of the abdominal aorta and occurs most commonly in ⩽9% of adults >65 years of age. The clinical approach to AAA is currently limited to surgical repair and is not indicated in patients with small AAA or who are asymptomatic. Pathological features of AAA include chronic vascular inflammation of the aortic wall, progressive extracellular matrix degradation, and increased neovascularization. Because of the high mortality rate associated with AAA, new effective therapeutic strategies are needed to prevent its progression.

Characteristics, timing of appearance of phenotype and phenotypic tests used (attach supporting data when unpublished if available):

Infusion of Angiotensin-II (AngII) into apoE knockout mice leads to the production of abdominal aortic aneurys. Delivery of AngII at doses of 1000 ng/kg per minute, via subcutaneously implanted osmotic mini-pumps, leads to abdominal aortic aneurysm in the suprarenal region within the 28-day infusion period. The characteristics of AngII-induced abdominal aortic aneurysms are consistent with an activation of an inflammatory response (macrophage accumulation) and the stimulation of a proteolytic cascade (elastin degradation) in the suprarenal aorta.

If applicable, Intervention(s) performed (type, dose, route of administration, frequency):

Eight-week-old male apoE-/- mice are used in these studies. An osmotic minipump (Alzet, Model 2004, Charles River) implanted subcutaneously in the dorsum of the neck was used to infuse Ang-II at a rate of 1000 ng kg-1 min-1 for 28 days.

Phenotype post-treatment (include null or negative results and attach supporting data separately):

At the end of the experimental protocols, mice are anesthetized and cut open ventrally. Left cardiac ventricles are perfused with phosphate-buffered saline (10 mL) with an exit through the severed right atrium. The aorta is exposed under a dissecting microscope, the periadvential tissue is removed and the aorta is photographed. Suprarenal regions of the abdominal aorta are identified between the last pair of intercostal arteries and the right renal branch. Maximal outer diameter of the suprarenal aorta is measured ex vivo using ImageJ software (NIH). Aneurysm severity (stage I to stage IV) is evaluated based on previous studies: Type I, dilated lumen in the suprarenal region of the aorta without thrombus or with a little thrombus; Type II, dilated lumen in the suprarenal region of the aorta with a pronounced bulbous form that contains thrombus; Type III, dilated lumen in the suprarenal region of the aorta with multiple aneurysms; Type IV, attributed to ruptured aneurysms. Necropsies are performed on all mice that died during the experimental treatment. Aortic rupture is defined as the observation of blood clots in either the retroperitoneal cavity (abdominal aortic rupture) . The ex vivo diameter of the ascending aorta and the intimal area of the thoracic aorta are measured.

Systolic blood pressure IS measured in conscious mice using a non-invasive tail-cuff system (Model LE5002 Pressure Meter, PANLAB, Barcelona, Spain) . Conscious mice were restrained on a warming chamber (Model LE5610, PANLAB). Mice are acclimatized to the instrument for at least one week before implantation of the osmotic pumps. To avoid variations in blood pressure due to day cycle, all measurements are carried out between 9 and 11 a.m.

Plasma lipid levels are measured in mice fasted overnight. Total cholesterol (TC), triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) are determined using enzymatic procedures (WAKO, St Louis, MI). Histological, PCR and western blot analysis are performed with the suprarenal aortas.

References (list below):

1: Martorell S, Hueso L, Gonzalez-Navarro H, Collado A, Sanz MJ, **Piqueras L.** Vitamin D Receptor Activation Reduces Angiotensin-II-Induced Dissecting Abdominal Aortic Aneurysm in Apolipoprotein E-Knockout Mice. Arterioscler Thromb Vasc Biol. 2016 Aug;36(8):1587-97. doi: 10.1161/ATVBAHA.116.307530. PMID: 27283745.

2: Escudero P, Navarro A, Ferrando C, Furio E, Gonzalez-Navarro H, Juez M, Sanz MJ, **Piqueras L.** Combined treatment with bexarotene and rosuvastatin reduces angiotensin-II-induced abdominal aortic aneurysm in apoE(-/-) mice and angiogenesis. Br J Pharmacol. 2015 Jun;172(12):2946-60. doi: 10.1111/bph.13098. PMCID: PMC4459015.