0199
Endoglin is required to maintain normal cardiac function in adult life
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Endoglin protein (also known as CD105) is a co-receptor for members of the transforming growth factor-β (TGFβ) superfamily of ligands, and regulates angiogenesis. Patients carrying mutations in the endoglin gene develop the inherited vascular dysplasia, Hereditary Haemorrhagic Telangiectasia (HHT). In light of the growing clinical interest in endoglin function in cardiovascular disease, we aimed to determine its role by depleting endoglin in a mouse model during adult life and assess effects on cardiac function. Endoglin was depleted in adult Rosa26-Cre-ERT2;Eng-/-/I1 mice using tamoxifen treatment to generate “ubiquitous” endoglin knockout (Eng-iKO) mice and cardiac magnetic resonance imaging (MRI) was used to evaluate cardiac function at 1, 3, 5 and 12 weeks after endoglin knockdown. Loss of endoglin leads to an enlarged heart and cardiomyocyte hypertrophy within 5 weeks and left ventricular volumes continued to enlarge substantially over subsequent weeks. However, LV ejection fraction was not significantly altered in Eng-iKOu mice compared with controls suggesting that cardiac function was not impaired. To address whether the cardiac remodelling observed in Eng-iKOu mice was due to loss of endoglin in endothelial cells we used a transgenic Cre line (Cdh5Cre-ERT2) to generate endothelial specific depletion of endoglin (Eng-iKOe). These mice showed a similar increase in heart mass and ventricular volumes to the Eng-iKOu mice. To investigate if vasomotor defects are contributing to the major cardiac remodelling, we analysed vasomotor function in the aortas of Eng-iKOe mice. We found an increased contraction response of the aorta to phenylephrine in Eng-iKOe mice compared to controls, suggesting that endoglin is important in controlling the aortic contractile response. These results describe a novel phenotype and highlight the importance of endothelial endoglin in the maintenance of cardiac structure and function.

0237
Gadd45γ promotes cardiac dysfunction by inducing necroptosis pathway in a mouse model of chronic myocardial infarction
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0149
Agonistic anti β3-adrenergceptor antibodies do not affect the β1-adrenergceptor-mediated inotropy and the β3 adrenergceptor-mediated vasorelaxation in Lewis rat
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Cardiac activity of autoantibodies (AABs) directed against β1-adrenoceptor (β1-AR) has been proposed to play an important role in the pathogenesis of dilated cardiomyopathy. Our previous work has shown that the immunization of rats with the second extracellular loop (ECII) of β1-AR induced endothelial dysfunction in aorta and mesenteric arteries. However, until now, no study has explored the cardiovascular effects of β1-AABs alone or combined with β3-AABs.

**Aim:** To evaluate whether β1-AABs possess β1-AR agonist effect and whether active immunization producing β1-AABs and/or β3-AABs has deleterious effects on cardiac and vascular reactivity in Lewis rats.

**Methods:** Lewis rats were immunized for 3 months with peptidic sequences corresponding to the ECII of β1-AR and/or β3-AR. The agonistic effect of β1-AABs was evaluated on electrically field-stimulated isolated cardiac myocytes from adult rabbit by measuring the cell shortening. Isotropy studies and isolated aorta and mesenteric artery studies were also conducted on immunized rats.

**Results:** SRS5611A (10 nM), a preferential β3-AR agonist and purified β3-AABs (25 μg/mL) induced a decrease of cell shortening (–39.6±4.4% (n=11) and –18.5±3.9% (n=10) respectively). This decrease was significantly inhibited when the cardiomyocytes were preincubated with the L-748337 (1 μM), a selective β3-AR antagonist (p<0.05). The cell shortening of cardiomyocytes from rats immunized against the β3-AR, in response to isoprenaline (10 nM), was significantly decreased (p<0.05). In contrast, this effect was conserved in rats immunized against β1-AR or β3/β1-AR. Vasorelaxations induced by acetylcholine and SRS5611A in both aorta and mesenteric arteries were unaltered by immunization.

These results show that β1-AABs induced a β1-AR agonist-like activity. They would not have a cardiovascular pathogenic action but would offset the cardiac and endothelial dysfunctions caused by β3-AABs.

**0393**

**Impact of miR-378* and its target desmin intermediate filament on mitochondria distribution in cardiomyocytes**

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**Background:** MiR-378 and miR-378* microRNAs are derived from an intron of the PGC-1β gene, a regulator of mitochondrial biogenesis. Their expression is either repressed or increased during heart failure depending on the model. Through proteomics approaches, we previously identified new targets of these miRs in H9c2 fetal cardiomyoblasts, among which lactate dehydrogenase for miR-378 and key cytoskeletal proteins for miR-378*.

**Aims:** To better assess its role in energy metabolism and differentiation; we overexpressed miR-378 and miR-378* in primary neonate rat cardiomyocytes (NRC) that are more differentiated and less proliferative than H9c2 myocytes (NRC) that are more differentiated and less proliferative than H9c2.

**Results:** We identified desmin as a new target of miR-378* in NRC. Desmin network plays a key role as a structural integrator of myofibrils and mitochondria positioning. MiR-378* overexpression reduced desmin levels and disrupted its organization. Confocal microscopy analysis of NRC stained with the mitochondrial dye MitoTracker revealed that miR-378* overexpression alters mitochondria distribution in the cell. AAV-mediated rescue of desmin expression in presence of miR-378* preserved mitochondria distribution.

Conclusion and perspectives: These results suggest that changes in miR-378* expression level could play an important role in the coupled alteration of cytoskeletal and mitochondrial networks observed in failing myocardium.

**0229**

**Alterations of cardiac function induced by postnatal overfeeding can be reversed by moderate diet restriction**

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Postnatal overfeeding (OF) in rodents induces a permanent moderate increase in body weight, metabolic disorders and progressive alterations of cardiac function. Our aim was to determine whether moderate diet restriction could restore cardiac function in mature overfed mice. Immediately after birth, litters of C57BL/6 mice were either maintained at nine (normal-fed group, NF), or reduced to three in order to induce OF. At weaning, mice of both groups received a standard diet ad libitum (AL). At 6 months of age, half of the OF mice were assigned to a moderate 20% calorie restriction (CR, OF-CR) for one month, while NF and the other half of the OF mice continued to eat ad libitum (NF-AL, OF-AL). Cardiac function was followed using echocardiography and, at 7 months, the sensitivity to ischemia-reperfusion injury was evaluated in isolated perfused hearts. Six-month-old OF mice weighed 22.5% more than NF mice. Left ventricular fractional shortening (LVFS) and ejection fraction (LVEF) were decreased in OF mice (25.5% vs. 30.5% for LVFS; 50% vs. 58% for LVEF, p<0.05). Left ventricular internal diameter in diastole (LVIDd) and systole (LVIDs) were significantly greater in OF than NF mice. One month of moderate CR normalized body weight in OF-CR compared with OF-AL (31.1 vs. 37.4 g, p<0.001). Moreover, LVEF was greater in OF-CR than OF-AL (61% vs. 52%, p<0.05) and became comparable to that in NF-AL. LVIDd and LVIDs were also normalized in OF-CR. Ex vivo, after 30 min of global ischemia, hearts isolated from OFCR mice showed better functional recovery than those of the two other groups. Our study suggests that short-term moderate diet restriction could normalize body weight gain induced by postnatal OF and, interestingly, could reverse alterations of cardiac function and susceptibility to myocardial ischemia-reperfusion injury in OF.