Cardiac activity of autoantibodies (AABs) directed against β_1-adrenoceptor (β_1-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 β_1-AR induced endothelial dysfunction in aorta and mesenteric arteries. However, until now, no study has explored the cardiovascular effects of β_3-AABs alone or combined with β_1-AABs.

Aim: To evaluate whether β_3-AABs possess β_3-AR agonistic effect and whether active immunization producing β_3-AABs and/or β_1-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 β_3-AR and/or β_1-AR.? The agonistic effect of β_3-AABs was evaluated on electrically field-stimulated isolated cardiomyocytes from adult rabbit by measuring the cell shortening. Inotropy studies and isolated aorta and mesenteric artery studies were also conducted on immunized rats.

Results: SR58611A (10 nM), a preferential β_3-AR agonist and purified β_3-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 β_3-AR antagonist ($p<0.05$). The cell shortening of cardiomyocytes from rats immunized against the β_1-AR, in response to isoprenaline (10 nM), was significantly decreased ($p<0.05$). In contrast, this effect was conserved in rats immunized against β_3-AR or β_3/β_1-AR. Vasorelaxations induced by acetylcholine and SR58611A in both aorta and mesenteric arteries were unaltered by immunization.

These results show that β_3-AABs induced a β_3-AR agonist-like activity. They would not have a cardiovascular pathogenic action but would offset the cardiac and endothelial dysfunctions caused by β_1-AABs.

0393

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

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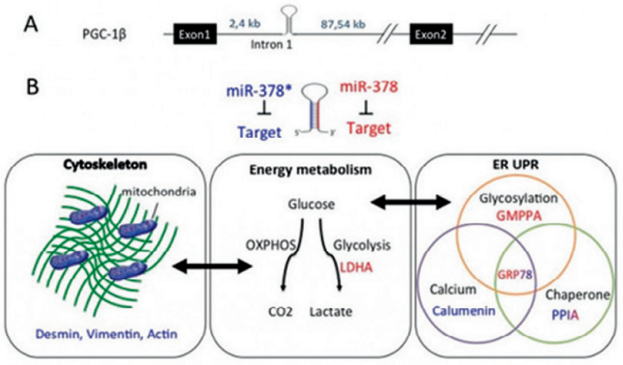
Background: MiR-378 and miR-378* microRNAs are derived from an intron of the PGC-1β gene, a regulator of mitochondrial biogenesis. Their expression is either repressed or increased during heart failure depending on the model. Through proteomics approaches, we previously identified new targets of these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

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. Mir-378 overexpression had a milder impact on cell organization than miR-378* and did not directly targetted desmin.

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.



Abstract 0393 – Figure: Biological functions regulated by miR-378/378*

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 OF*CR* 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.