DYSREGULATED EXPRESSION OF ANKYRIN REPEAT DOMAIN 1 IN THE DEVELOPING MYOCARDIUM CAUSES ANOMALOUS VENOUS RETURN AND MORPHOGENETIC DEFECTS BY IMPAIRING CARDIAC REMODELLING

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Introduction. Total anomalous pulmonary venous return (TAPVR) is a severe congenital heart disease characterized by failure of pulmonary veins to connect exclusively to the left atrium. Cardiac Ankyrin Repeat Protein (CARP), encoded by the Ankyrin repeat domain 1 (Ankrd1) gene, is a mechanosensor protein, involved in physiological and pathological remodelling of myocardium. Recently, we have identified Ankrd1 as a candidate gene for TAPVR in isolated patients. Our reported TAPVR patients presented either increased Ankrd1 transcript levels or a missense T116M mutation, resulting in greater protein stability. To date, the role of this gene in venous pole development, as well as the link between an Ankrd1 gain of function condition and TAPVR pathogenesis in humans remain unexplored.
Methods. Two transgenic mouse lines overexpressing wild-type (WT) CARP or T116M-CARP, under the control of the α–MHC promoter, have been previously generated. Embryos from control and transgenic mice have been harvested at 10.5 and 14.5 days post coitum and processed to perform morphological and expression analyses.
Results. Our results showed that Ankrd1 expression delineates discrete morphogenetic subdomains in the developing heart of controls. Myocardial overexpression of WT-CARP or T116M-CARP resulted in strong impairment of early cardiac remodelling steps, including rotation and cranial expansion of the sinoatrial region. Mid-fetal transgenic hearts presented complex morphogenetic defects and abnormal pulmonary venous connections, accompanied by strong alteration of structural properties, but not of the molecular patterning program. Additionally, cardiac chamber trabeculation was more extended.
Conclusions. Our data indicate that CARP is a critical sensor-signalling molecule that modulates cardiomyocyte cellular properties during development. Moreover, Ankrd1 regionalized expression is required to refine shape and relative position of cardiac compartments and increased WT-CARP or T116M-CARP levels lead to TAPVR by impairing remodelling of early venous pole myocardium. These findings uncover novel levels of complexity in genetic regulation of cardiac development.

CHOLESTEROL EFFLUX CAPACITY MODULATION BY THE NUTRACEUTICAL COMPOUND "OLEACTIVE®"

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Aim. In the last decades, the use of nutraceutical compounds to support or replace medical therapies is spreading, due to fewer side effects, and more tolerability by patients compared to traditional drugs. Nutraceutical compounds may contribute to the qualitative and quantitative modulation of lipid and lipoprotein profile. HDL are the responsible of cholesterol efflux from the atherosclerotic plaque, through the interaction with cholesterol transporters expressed in macrophages composing the atheroma. Recent studies have shown the inverse correlation between the cholesterol efflux capacity of the serum (CEC), mostly mediated by HDL, and cardiovascular risk. The aim of this study is to evaluate the effects of the Oleactive® compound on lipid and lipoprotein profile in golden Syrian hamsters. In particular, ABCA1 mediated efflux has been evaluated, as it is the main transporter involved in cholesterol efflux from macrophages. Oleactive® is a nutraceutical compound patented by Fytexia company (Vendres, France). Experimentations are part of an industrial project, which is not finalized yet and the Oleactive® composition is secreted.
Material and Methods. 40 Golden syrian hamsters were divided in 4 groups. Standard group (STD group), which followed normolipidic diet, received daily vehicle for 12 weeks. The remaining groups, fed with a hypercholesterolemic diet(2g/kg of cholesterol), received daily vehicle (CTRL group), Atorvastatin (1.23 mg/kg/day-Atorva group), or Oleactive® formulation (OLA group) for 12 weeks. After sacrifice, HDL, total cholesterol (TC), LDL, triglycerides (TG) of the plasma were analyzed. We analyzed the ABCA1 mediated efflux and passive diffusion using murine macrophages J774 treated with cpt-cAMP, which induces an overexpression of ABCA1 transporter. Afterwards cells were incubated with sera (1%, v/v).
Results. Lipid profile of OLA group showed differences compared to CTRL group. In detail, it has been observed a slightly decrease of total cholesterol(-1,04mmol/L), LDL-C(1,14 mmol/L) and a significant decrease of triglycerides(-1,21mmol/L). Conversely, HDL-C levels are similar in two groups. Atorva group showed an increased plasma total cholesterol (+4,02mmol/L,$p<0.05$) reduction of total body weight, fat mass and BMI, without any significant difference between the two diets [body weight: -2.0 kg (-2.5%) vs. -2.4 kg (-3.0%)], [fat mass: -1.8 kg (-6.1%) vs. -1.6 kg (-5.6%)] [BMI: -0.7 kg/m^2 (-2.4%) vs. -0.8 kg/m^2 (-2.8%)], for Med and Veg, respectively. With regard to circulating biomarkers, Veg determined a significant ($p<0.05$) decrease for total cholesterol [-6.0 mg/dL (-2.9%)], LDL cholesterol [-6.5 mg/dl (-5.1%)] and insulin levels [-0.7 mU/L (-6.9%)], while Med determined a significant reduction of triglycerides [-11 mg/dL (-8.9%)].
Conclusions. Our results show that the administration of Olective® influence the lipid profile in hamsters, which have a lipid and lipoprotein profile more akin to the human one, compared to other animal models. In addition, the increased CEC, due to an increased ABCA1 mediated efflux by Oleactive®, may be a potential mechanism against atherosclerotic diseases. The administration of this nutraceutical compound could be used as support of pharmaceutical therapy, or in case of light hypercholesterolemia.