**Topic 25 – Heart failure, cardiomyopathy – E**

April 03rd, Friday 2015

**0307**

QSOX1 has a protective role in the myocardium face to acute stress

Arthur Cescau (1), Anaïs Caillard (1), Malha Sadoune (2), Zhenlin Li (5), Mebazaa Alexandre (4), Nicolas Vodovar (2), Agnès Charbonnel (5), Iane Lise Samuel (2), Damien Logeart (1), Alain Cohen Solal (1), Lise Samuel (2), Damien Logeart (1), Alain Cohen Solal (1)

Introduction: QSOX1 was identified as a plasma biomarker of acute heart failure (AHF). QSOX1 being a sulfhydril oxidase, our aim was to decipher the role of QSOX1 in the heart face to an AHF event.

Methods: AHF was provoked by IP injections of Isoproterenol (ISO, 300mg/kg/12h) for 2 days in mice (C57Bl/6 J) whereas control (C) received NaCl 0.9%. Mice were killed at day 3, after echocardiography. QSOX1 KO (C57Bl/6 J) mice were generated using a YG021tm1a embryonic stem cell clone (KOMP). The KO construct contains a promoter-less lacZ gene under the control of the QSOX1 regulatory sequences. The mRNA levels were analyzed by RT-qPCR. The cellular level of oxidative stress was detected by using DHE. Fibrosis was analysed by Sirius red and collagen mRNA.

Results: At baseline QSOX1+ adult mice did not display any cardiac or vascular phenotype. After ISO, lacZ expression dramatically increased in QSOX1 KO hearts with the strongest β-galactosidase staining in the atria. In mice receiving ISO, a pulmonary congestion, BNP (x2 p<0.001) and CD68 (x3, p<0.001) increases were observed only in QSOX1-/-, whereas Galectin 3 increased in both groups. After ISO, the severe cardiac dysfunction in response to acute cardiac stress by ISO (x3, p<0.001) increases were observed only in QSOX1-/-, whereas Galectin 3 increased in both groups. Hence, our data indicated that QSOX1 protects the heart in response to acute stress.

Conclusion: We provided evidence that the absence of QSOX1 leads to a more serious cardiac dysfunction in response to acute cardiac stress by ISO than in WT counterparts. Hence, our data indicated that QSOX1 protects the heart in response to acute stress.

**0313**

Impact of overweight on anthracline and trastuzumab-induced cardiotoxicity: experimental study in mice

Eve Rigel (1), Olivier Hachet (2), Charles Guenancia (1), Mona Aboutabl (3), Na Li (1), Yves Cottin (4), Luc Lorgis (4), Luc Rochette (1), Catherine Vergely (1)

**0152**

Effects of connexin 43 inhibition on mitochondrial function in cardiac skinned fibers and isolated mitochondria

Dominique Detaillle, Angela Machado-Vieira, Philippe Dioslez, Thomas Desplantez

University de Bordeaux, IHU Institut de Rythmologie et Modélisation Cardiaque, INSERM U1045 CRC/TB, Bordeaux, Pessac, France

Connexin 43 (Cx43) is a main component of intercellular gap junction channels in cardiomycocytes. The presence of Cx43 in heart mitochondria has been also reported, where it may participate in energy metabolism and protein trafficking, cellular signal transduction and protein degradation. We have developed a transgenic model to overexpress PDZRN3 in cardiomycocytes around birth by crossing a ptRE-PDZRN3-V5 mice with MHC-ITA mice (MHC/PDZRN3-V5). As analyzed by echocardiography and histology, 100% of mutant mice developed a dilated cardiomyopathy between 2-4 weeks of life, with an EF around 40% and a poor survival after 2 months. As analyzed by immunohistochemistry and Western blot, we found a dramatic loss of Cx43 expression at the ID as soon as 15 days after birth together with a robust nuclear expression of Z01. This was associated with an alteration of myocyte survival, impairment in myocyte architecture and a progressive ventricle fibrosis starting after 3 weeks.

This case reveals a novel role of the Wnt/Po/PDZRN3 signaling in the coordination and the polarized organization of Intericolated Discs.

**0331**

Pathophysiology of the ubiquitin ligase E3, PDZRN3, in the development of dilated cardiomyopathies

Mathieu Pernot (1), Laura Cetrin (2), Béatrice Vinassa (3), Thierry Couffinhal (2), Cécile Dupla (3)

(1) CHU Bordeaux, Chirurgie cardiovasculaire, Pessac, France – (2) CHU Bordeaux, Maladies Cardiaques et Vasculaires, Pessac, France – (3) CHU Bordeaux, Hôpital Haut-Lévêque, INSERM, Adaptation cardiovasculaire à l’schéme, U1034, Pessac, France

Dilated cardiomyopathy is a major cause of heart failure with a poor prognostic. Molecular mechanisms underlying the transition toward the dilated phenotype are still not known. In heart, individual cardiomyocytes connect some with the others via their extremities by junctional platform (Intericolated Discs, ID) crucial for the mechanical coupling and the anisotropic conduction of the electric signal.

In this project, we are interested in an Ubiquitine ligase E3 called PDZRN3, which is expressed and regulated in cardiomyocytes during their maturation. We have previously identified PDZRN3 involvement in the Wnt Planar Cell Polarity (Wnt/PCP) signaling in vascular morphogenesis.

In the heart, the ubiquitine proteasome system plays a fundamental role in the regulation of protein quality control in cells whereby it regulates main processes as protein trafficking, cellular signal transduction and protein degradation.

We have developed a transgenic model to overexpress PDZRN3 in cardiomyocytes around birth by crossing a ptRE-PDZRN3-V5 mice with MHC-ITA mice (MHC/PDZRN3-V5). As analyzed by echocardiography and histology, 100% of mutant mice developed a dilated cardiomyopathy between 2-4 weeks of life, with an EF around 40% and a poor survival after 2 months. As analyzed by immunohistochemistry and Western blot, we found a dramatic loss of Cx43 expression at the ID as soon as 15 days after birth together with a robust nuclear expression of Z01. This was associated with an alteration of myocyte survival, impairment in myocyte architecture and a progressive ventricle fibrosis starting after 3 weeks.

This study reveals a novel role of the Wnt/PCP/PDZRN3 signaling in the coordination and the polarized organization of Intericolated Discs.

© Elsevier Masson SAS. All rights reserved.
cardiotoxicity, and no study has already evaluated the impact of moderate overweight on the cardiotoxic effect of DOX alone or in combination with TRZ.

Immediately after birth, litters of C57BL/6 mice were either maintained at 10 (normal litter, NL), or reduced to 3 (small litter, SL) in order to induce programming of ~15% overweight through postnatal overfeeding. At 4 months, in order to evaluate the potentiation of DOX cardiotoxicity by TRZ, NL and SL mice received a single intraperitoneal injection of either saline, DOX (6mg/kg), TRZ (10mg/kg) or the combination of both (DOX-TRZ). Trans-thoracic echocardiography was performed 24 hours before, 10 and 20 days after treatments, in order to evaluate the evolution of cardiac function.

Twenty days after DOX administration, systolic dysfunction was observed only in overweight-SL group, while NL mice group kept a preserved left ventricular ejection fraction (LVEF). Moreover, in NL group, the function impairment appeared when TRZ was co-administrated. 48 hours after drug administration, gene expression of Erb-B2, the murine analog of HER2, was induced in the myocardium of DOX-treated mice, and its induction was potentiated by co-treatment with TRZ. Expression of natriuretic peptides (ANP, BNP) appeared to be potentiated in DOX-TRZ mice of both NL and SL groups, whereas the expression of b-MHC increased significantly in overweight-SL mice.

In an acute model of DOX cardiotoxicity, moderately overweighted adult mice are more sensitive to cardiac systolic impairment. Moreover, our results show an early myocardial induction of TRZ-receptor after DOX and/or TRZ, and confirm the potentiating action of TRZ on DOX-induced cardiotoxicity in mice.