Topic 25 – Heart failure, cardiomyopathy – E

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0307

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

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Introduction: QSOX1 was identified as a plasma biomarker of acute heart failure (AHF). QSOX1 being a sulfhydryl 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 9‰. Mice were killed at day 3, after echocardiography. QSOX1 KO (C57Bl/6 J) mice were generated using a QSOX1tm1a 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$^{+/-}$ 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 QSOX1$^{-/-}$ mice was associated with signs of enhanced oxidative stress (DHE staining $p<0.0001$). An early fibrosis was observed by Sirius red analysis and associated with an increase of collagen 1 and 3 mRNAs without difference between WT and QSOX1$^{-/-}$ mice.

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.

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

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Connexin 43 (Cx43) is a main component of intercellular gap junction channels in cardiomyocytes. The presence of Cx43 in heart mitochondria has been also reported, where it may participate in energy metabolism and protection against ischemia. Given the key role for mitochondria in pathogenesis of heart diseases, we examined how mitochondrial function could be altered in case of Cx43 pharmacological inhibition by carbenoxolone (CBX). Oxygen consumption rates under various substrate conditions were determined either in ventricles from pig hearts using saponin-permeabilized fibers, or in isolated mitochondria from rat hearts. Measurements of mitochondrial membrane potential ($\Delta\Psi$) and reactive oxygen species (ROS) by fluorescence, as well as calcium-induced matrix swelling by light scattering were recorded in cardiac mitochondria exposed to increasing CBX concentrations. At high dose (100µM), CBX substantially decreased the ADP-stimulated respiration while increasing mitochondrial protons leak in permeabilized ventricular fibers. In isolated mitochondria, we found a similar response accompanied by a collapse of $\Delta\Psi$ and ROS production. At lower CBX concentrations (≤25µM), the substrates oxidation rates by mitochondria were not changed (except for ADP-stimulated complex I respiration which was slightly reduced), but $\Delta\Psi$ remained stable. More interestingly, low CBX concentrations increased calcium sensitivity of mitochondria when incubated in a KCl versus sucrose medium. This phenomenon was partly prevented by cyclosporin A, an inhibitor of the permeability transition pore (PTP) involved in apoptosis. These data suggest a possible interaction between the function of Cx43 and the mitochondrial PTP. Further investigations will resolve the impact of Cx43 on bioenergetics in order to better understand some mitochondrial disorders in failing hearts.

0331

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

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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 (Intercalated 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 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 αMHC-tTA 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 Intercalated Discs.

0131

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

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Trastuzumab (TRZ), a humanized monoclonal antibody against Human Epidermal Growth Factor Receptor 2 (HER2) oncogene, is believed to potentiate doxorubicin (DOX) cardiotoxicity, resulting in left ventricular dysfunction. Few data indicate that overweight could influence DOX-induced