OE-405

Peroxisome Proliferator-Activated Receptors (PPARs) and PPARγ Coactivator-1 Are Expressed Synergetically in Patients with Dilated Cardiomyopathy and Severe Left Ventricular Failure

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Background: Peroxisome proliferator-activated receptor (PPAR) is a transcriptional regulator of cardiac energy metabolism. However, expression of PPAR in the human failing heart has not been fully examined. PPARγ coactivator-1 (PGC-1) is a nuclear receptor/ transcriptional coactivator that induces mitochondrial proliferation and respiratory function in the heart and myogenic cell lines. We hypothesized that the expression of PPARs and PGC-1 might be increased in human failing cardiomyocytes. **Methods:** We examined the expression of PPARα, PPARγ and PGC-1 in 8 dilated cardiomyopathy (DCM) patients with decompensating heart failure by semi-quantative RT-PCR. PPARγ was also detected by immunohistochemical methods. Left ventricle (LV) samples were taken at left ventricular assist device (LVAD) implantation (n=7) or at heart transplantation (n=1) including 3 samples at autopsy 12 months after LVAD support. Normal LV samples of 2 autopsies were examined as controls. **Results:** RT-PCR showed expression of PPARα and PPARγ associated with PGC-1 in all DCM patients. Numerous nuclei of cardiomyocytes showed positive immunoreactivity against PPARγ. Moreover, expression of PPARα, PPARγ and PGC-1 was markedly decreased after LVAD support. Expression levels of PPAR and PGC-1 were very low in contorl LVs. **Conclusion:** Both PPARs and PGC-1 were expressed in cardiomyocytes of DCM patients and decreased after load reduction. Upregulation of PPAR expression combined with PGC-1 may be involved in the altered energy metabolism of heart failure.

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Localization of Coxsackievirus and Adenovirus Receptor (CAR) in Rat Heart

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Background: coxsackievirus B is the most common cause of viral myocarditis and particularly virulent in the neonate and child. Adenoviruses also cause myocarditis. Recently coxsackievirus and adnovirus receptor (CAR) was identified and we reported that CAR was expressed in rat heart. However its precise localization has been unknown. **Methods:** Rats were sacrificed at birth, at the age of 1 week, 1 month, and more than 3 months, and the hearts were removed. They were fixed in Bouin's liquid and embedded in paraffin. Sliced sections were stained by immunohistochemistry (IHC) using two different polyclonal anti-CAR antibodies with and without a high-temprature-heating antigen retrieval technique (AR). Western blotting analysis (WB) was also done using the same antibodies. **Results:** Without AR, adult rat heart was negative for CAR by IHC, although WB indicated the presence of CAR. With AR, CAR was clearly stained on intercalated disks of adult cardiomyocytes. In contrast, it was stained on whole surface of neonatal cardiomyocytes. **Conclusions:** CAR was localized on whole surface of neonatal cardiomyocytes, and on intercalated disks of adult cardiomyocytes. The localization may have relation with virulency of viral myocarditis.

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Induction of Cardiac Hypertrophy in Severe Combined Immunodeficiency Mice by Transfer of Lymphocytes from Patients with Congestive Heart Failure

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Background: We have described that autoantibodies against sarcolemmal Na-K-ATPase were present in sera from patients with idiopathic dilated cardiomyopathy (DCM) or patients with paroxysmal atrial fibrillation (PAF) with congestive heart failure (CHF). **Objective:** To elucidate long-term effects of lymphocyte transfer from patients with CHF into severe combined immunodeficiency (SCID) mice. **Method:** Thirty-five CB-17 SCID (6-9 weeks old) mice were injected intraperitoneally 25 million peripheral blood lymphocytes (PBL) from CHF patients who have autoantibodies against sarcolemmal Na-K-ATPase (n=25) or PBL from healthy control donors (n=10, CTL group). CHF patients with autoantibodies divided into 2 groups: CHF patients with DCM (n=13, DCM group) or PAF patients with non-DCM (n=6, PAF group). ELISA and morphological studies were performed six months after the transfer. **Results:** ELISA indicated that autoantibodies titer directed against Na-K-ATPase were low. One mouse in DCM group died of CHF on 139 days after the transfer. Heart/body weight ratio (mg/g) was higher in DCM group (4.44±0.41, $p<.01$) and in PAF group (4.37±0.28, $p<.01$), compared to the CTL group (4.07±0.41). **Conclusion:** Transfer of the PBL from CHF patients with autoantibodies was able to induce cardiac hypertrophy in SCID mice. These data suggest that autoimmune mechanism via Na-K-ATPase play a role in the pathogenesis of CHF.

OE-408

Evidence for the Regulatory Role of Fas/Fas Ligand Interaction during the Subacute Stage of Myocardial Infarction for Post-Infarct Heart Failure

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We previously reported the post-infarct gene therapy with soluble Fas (sFas) improved ventricular remodeling and dysfunction during the chronic stage of myocardial infarction (MI). One of the mechanical explanations for the beneficial effects was apoptosis inhibition of granulation tissue cells. In the present study, we attempted to reinforce this working hypothesis. Treatment with adenovirus encoding sFas (Ad.CAG-sFas) on the 3rd day of MI of mice significantly improved ventricular remodeling and dysfunction during the chronic stage of MI (4 week-MI) as previously reported. This treatment accompanied a significant suppression of apoptosis of granulation tissue cells during the subacute stage of MI. However, when the gene was delivered on the 3 weeks post-MI where granulation tissue cells were almost cleared during the natural course of infarct healing, the beneficial effects on ventricular dilatation and dysfunction were not observed after the further 4 weeks. In the next experiment, apoptotic rate of the granulation tissue cells was significantly fewer in mice lacking functioning Fas (lpr/lpr strain) and in those lacking Fas ligand (gld/gld strain) compared with that of control mice (C57BL/6J), and post-infarct ventricular remodeling and dysfunction were greatly attenuated in these strains. These findings support the critically regulatory role of Fas/Fas ligand interaction during the subacute stage of MI for progression of post-infarct ventricular remodeling and dysfunction.