S9-2

In vivo and in vitro muscle metabolic profiles of TIEG1 KO muscle mice using spectroscopy techniques (MRS/NMR)

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Introduction: TGFbeta inducible early gene-1 (TIEG1) is a member of the Krüppel-like family of transcription factors (KLF10). Deletion of TIEG1 results in muscle fiber hypertrophy, texture profile changes, dysfunction of mitochondrial biogenesis and defects in functional properties.
Aim: To further analyze the effect of TIEG1 gene on muscle metabolism.
Methods and Results: 12 WT and 12 TIEG1 KO mice were used for in vivo spectroscopy acquisitions 9.4T (Bruker). A home built coil was developed. Resonance frequencies were 400 MHz for the proton and 162 MHz for the phosphorus. Localized 1H and 31P spectroscopy were performed with PRESS sequence providing quantification of different metabolites. While 1H-NMR spectra showed no significant difference for choline, creatine, taurine and extramyocellular lipids between WT and TIEG1 KO. 31P spectra revealed a significant difference for phosphocreatine and ATP. For metabolomics analysis 1H-NMR spectra were obtained from soleus (N = 18) and EDL (N = 18) muscles isolated from WT and TIEG1 KO with a 600 MHz spectrometer (Bruker, 14T). Heatmaps were generated to visually depict changes in metabolites ($p < 0.05$) as a function of mouse genotype. For both TIEG1 KO soleus and EDL muscles, there were more down regulated metabolites compared to WT muscles.
Conclusion: The present study has demonstrated a new role for TIEG1 in the homeostasis of the muscle metabolome and specifically in energetic metabolism.

S9-4

The missense E258 K-MyBP-C mutation increases the energy cost of tension generation in both ventricular and atrial tissue from HCM patients

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Mutations in MYBPC3, the gene coding for cardiac myosin-binding protein-C (cMyBP-C) are the most common cause of Hypertrophic CardioMyopathy (HCM). The E258K-MyBP-C is a highly penetrant missense mutation with poorly understood molecular mechanisms. Mechanics and kinetics of contraction as well the energetic cost of tension generation were investigated using left ventricular (LV) and atrial tissue from three E258K HCM patients and compared to those from controls (donor hearts, aortic stenosis patients, and HCM patients negative for sarcomeric protein mutations). Kinetics of tension generation and relaxation were measured in single LV and atrial myofibrils mounted in a force recording apparatus (15 °C), maximally Ca^{2+}-activated (pCa 4.5) and fully relaxed (pCa 9.0) by rapid solution switching (< 10 ms). Maximal ATPase and isometric active tension were simultaneously measured in Triton-permeabilized LV strips. In E258K, maximal tension of atrial myofibrils was reduced compared to controls, while maximal tension of LV myofibrils was unchanged. The rate of tension generation following maximal Ca^{2+} activation (kACT) was faster in both ventricular and atrial E258K myofibrils compared to controls. The rate of isometric relaxation (slow kREL) was also faster in E258K myofibrils, suggesting faster cross-bridge detachment and increased energy cost of tension generation. Direct measurements in ventricular skinned strips confirmed that tension cost was higher in E258K preparations compared to controls. We conclude that the E258K mutation primarily alters apparent cross-bridge kinetics and impairs sarcomere energetics. In vitro, the mutation seems to induce similar kinetic and energetic effects in both atrial and LV sarcomeres. The smaller impact of the mutation on atrial muscle function compared to LV muscle in vivo is likely due to the different loading conditions of the two chambers.

S9-5

Role of PGC-1α associated mitochondrial biogenesis in statin-induced myotoxicity

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Background: Statins impair expression of PGC-1α in human and rat skeletal muscle, suggesting a role of PGC-1α in statin-induced myotoxicity.
Objective: This study aimed to investigate these effects in differentially expressed PGC-1α mouse models.
Methods: We used 3 mouse models: mice with muscle PGC-1α knockout (MKO), mice overexpressing PGC-1α (MCK), and wild-type (WT) mice. Mice treated for 3 weeks with water or simvastatin (5 mg/kg/d) by oral gavage, were assessed with grip test, metabolic treadmill and glucose tolerance test. We measured mitochondrial respiration and H2O2 production in fresh permeabilized muscle fibres.
Results: Simvastatin showed impairment in WT mice, manifested by decreased exercise capacity, glucose intolerance, and decreased mitochondrial respiration in the glycolytic muscle coupled with increased H2O2 production. MKO mice treated with simvastatin, showed decreased exercise capacity and mitochondrial respiration in oxidative and glycolytic muscle types. MCK mice showed no impairments of mitochondrial function and physical capacity.
Conclusion: Oxidative muscles are more resistant to simvastatin-associated toxicity than glycolytic muscles. PGC-1α seems to be a susceptibility factor and has an important role in mitigating of simvastatin induced myotoxicity.

S9-6

Single cell analysis reveals the involvement of the long non-coding RNA Pvt1 in myofiber metabolism modulation

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Long non-coding RNAs (lncRNAs) are emerging as important players in the regulation of several aspects of cellular biology. For a better comprehension of their function it is fundamental to determine their