Symposium- Parallel Symposium Mitochondria
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CK2-dependent phosphorylation in skeletal muscle regulates neuromuscular junction stability and mitochondrial homeostasis
Said Hashemolhosseini (GERMANY)

Protein kinase CK2, a pleiotropic serine/threonine kinase, plays an important role in many different biological processes inside of cells (Cozza *et al.* 2012). Conditional muscle-specific CK2 mutant mice lack grip strength and show muscle fatigability (Cheusova *et al.* 2006). We identified the role of CK2 in skeletal muscle cells as a regulator of neuromuscular junction maintenance by phosphorylation of different protein members of the postsynaptic apparatus (Herrmann *et al.* 2015). Moreover, CK2 is involved in ensuring proper mitochondrial homeostasis in skeletal muscle fibers by fine-tuning mitochondrial protein import through the translocase of the mitochondrial outer membrane. In absence of CK2-dependent phosphorylation of mitochondrial outer membrane translocase proteins, muscle fibers undergo accelerated mitophagy, as demonstrated by an up-regulated PINK/Parkin/p62 pathway.

Cheusova, T., Khan, M. A., Schubert, S. W. et al. (2006) Casein kinase 2-dependent serine phosphorylation of MuSK regulates acetylcholine receptor aggregation at the neuromuscular junction. *Genes Dev,* **20,** 1800-1816.
Cozza, G., Pinna, L. A. and Moro, S. (2012) Kinase Ck2 inhibition: AN update. *Current medicinal chemistry*.
Herrmann, D., Straubinger, M. and Hashemolhosseini, S. (2015) Protein Kinase CK2 Interacts at the Neuromuscular Synapse with Rapsyn, Rac1, 14-3-3gamma, and Dok-7 Proteins and Phosphorylates the Latter Two. *J Biol Chem,* **290,** 22370-22384.

GDF-15 is elevated in children with mitochondrial diseases and is induced by mitochondrial dysfunction
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We previously described increased levels of growth and differentiation factor 15 (GDF-15) in skeletal muscle and serum of patients with mitochondrial diseases. Here we evaluated GDF-15 as a biomarker for mitochondrial diseases affecting children and compared it to fibroblast-growth factor 21 (FGF-21). To investigate the mechanism of GDF-15 induction in these pathologies we measured its expression and secretion of in response to mitochondrial dysfunction.
We analysed 59 serum samples from 48 children with mitochondrial disease, 19 samples from children with other neuromuscular diseases and 33 samples from aged matched healthy children. GDF-15 and FGF-21 circulating levels were determined by ELISA.
Our results showed that in children with mitochondrial diseases GDF-15 levels were on average increased by 11-fold (mean 4046pg/ml, 1492 SEM) relative to healthy (350, 21) and myopathic (350, 32) controls. The area under the curve for the receiver operating- characteristic curve for GDF-15 was 0.82 indicating that it has a good discriminatory power. The overall sensitivity and specificity of GDF-15 for a cut-off value of 550pg/mL was 67.8% (54.4%-79.4%) and 92.3% (81.5%-97.9%) respectively.
We found that elevated levels of GDF-15 and or FGF-21 correctly identified a larger proportion of patients than elevated levels of GDF-15 or FGF-21 alone. GDF-15, as well as FGF-21, mRNA expression and protein secretion were significantly induced after treatment of myotubes with oligomycin and that levels of expression of both factors significantly correlated.
Our data indicate that GDF-15 is a valuable serum quantitative biomarker for the diagnosis of mitochondrial diseases in children and that measurement of both GDF-15 and FGF-21 improves the disease detection ability of either factor separately. Finally, we demonstrate for the first time that GDF-15 is produced by skeletal muscle cells in response to mitochondrial dysfunction and that its levels correlate in vitro with FGF-21 levels.

Mitochondrial complex I deficiency in mitochondrial disorders

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Mitochondrial disorders are both clinically and genetically heterogeneous and result from respiratory chain deficiencies leading to insufficient ATP production from oxidative phosphorylation (OXPHOS). These disorders are associated with mitochondrial DNA or nuclear gene mutations. Complex I (CI) is the largest enzyme of the OXPHOS system. In mammals it comprises 44 subunits with a total molecular mass of about 1 MDa. Moreover, its assembly requires at least 10 factors. Isolated CI deficiencies represent a frequent cause of mitochondrial disorders and lead to various clinical presentations. During the last 10 years, mutations in genes encoding CI subunits or assembly factors have been progressively identified by various approaches. Interestingly, most of these assembly factors were identified by the study of patients with mitochondrial CI deficiencies but lacking mutations in any known CI subunit. Whereas, the exact function of these factors is not completely known, study of patients fibroblasts has progressively allow to describe the pathway of assembly of this large complex.