Hereditary motor-sensory neurophaty 1X (HMSN 1X) occurs in 13.3% of all HMSN cases in the Republic of Bashkortostan. Four GJB1 mutations were described in 25 families with HMSN 1X: p.Arg22Gln (c.65G>A), p.Thr86Ile (c.257C>T), p.Pro87Ala (c.259C>G), p.Arg220Stop (c.658C>T). The most common mutation was p.Pro87Ala (c.259C>G). The clinical manifestations in the families with GJB1 mutations included progressive distal muscle atrophy and weakness, reduced sensation of proprioception, areflexia, sensitive ataxia and bilateral pes equinovarus or pes cavus deformity. The postural tremor of hands was the most common additional symptom. The disease of male patients begins in their first or second decade of life and was characterized by more severe impairment of the peripheral nerves with mild clinical CNS involvement. The disease's onset of female patients ranged from their first to fourth decade of life. Their clinical picture was presented by milder impairment of the peripheral nerves. Some of female patients have not any complaints in their health, but their physical examination shows the absence of the Achilles reflexes. Median motor condution velocity (MCV) ranged from 21.0 to 49.3 m/s. The most of female patients had median MCV more than 38 m/s, what was considered as HMSN, type II. In these cases mutation analysis in the GJB1 gene helps to confirm the genetic diagnosis of HMSN 1X and provide genetic counseling.

Hereditary motor-sensory neuropathy 1X, Charcot-Marie-Tooth disease, GJB1 gene

Hereditary neuropathies- #2529

P13- 211- Rigid spine syndrome associated with sensory-motor axonal neuropathy resembling Charcot-Marie-Tooth (CMT) disease are characteristic of BAG3 gene mutations.

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BAG3 (Bcl-2 associated athanogene-3) mutations have been described in rare cases of rapidly progressive myofibrillar myopathies beginning in the first decade with axial involvement, contractures and associated with cardiac and respiratory impairment occurring in the second decade. Axonal neuropathy has been documented in some patients, but usually not as a key clinical feature.

We report here a 22 year old patient with rigid spine syndrome and sensory-motor axonal neuropathy resembling Charcot-Marie-Tooth disease, without cardiac involvement.

A 22 year-old female from Gabon born to non-consanguineous parents developed at 10 years of age lower limb weakness, with inability to run and maintain prolonged staining. She walked with a stick and was wheelchair bound respectively at 14 and 17 years of age. Meanwhile she developed rapidly progressive spine deformity with hyperlordosis, starting at 15 year old. Her clinical examination showed severe rigid spine syndrome, associated with lower limb contractures affecting neck, hip, knee and ankles. She also had varus foot deformity. There was a marked proximal and distal weakness of lower limbs. Upper limb muscle strength was rather preserved. There was bilateral scapular winging. Tendon reflexes were absent. Sensory testing was normal. She also had hypophonia. Nerve conduction showed a severe sensory-motor neuropathy predominant in the lower limbs. Lower limb muscle MRI showed severe fat infiltration without specific pattern. Spine and brain MRI were normal. Creatine kinase (CK) levels were normal. Deltoid muscle biopsy performed at 19 years of age showed neurogenic pattern, along with discrete myofibrillar abnormalities. Forced vital capacity (FVC) was 42% of the predicted value. At 22 years of age, her electrocardiogram and transthoracic echocardiography were normal. Genetic analysis performed on a large panel comprising 45 CMT genes showed no mutation. Since the rigid spine syndrome worsened over the years, BAG3 gene was screened and the previously reported c.626C>T, pPro209Leu, mutation was identified.

This report confirms that rigid spine syndrome and sensory-motor axonal neuropathy resembling Charcot-Marie-Tooth disease are key clinical features of BAG3 gene mutations, which should be screened even without cardiac involvement. This diagnosis is of great importance since patients with BAG3 mutations require a close monitoring of cardiac function, given that BAG3 is a risk factor of cardiomyopathy and heart failure.

Rigid spine, sensory-motor axonal neuropathy, Charcot-Marie-Tooth disease, BAG3

P14- Homeostasis in the adult muscle/- N° 212 to N° 218

Homeostasis in the adult muscle- #2506

P14- 212- Investigation of Telomeres and Associated Proteins (TRF2) in a post-mitotic model; Muscle.

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The current view of telomere function relies on their ability to prevent DDR activation at chromosome ends. Telomere dynamics have been well studied and trends nowadays use them as the mitotic clock of cells and tissues (Daniali et al., 2013). Hence, making telomere shortening a Hallmark of aging (López-Otín et al., 2013). Interestingly, evidences that telomere signaling can be uncoupled from DDR and linked to the ability of telomere capping factors to behave as genome-wide transcriptional regulators are emerging (e.g., extra-telomeric binding sites; Martínez et al., 2014, Biroccio et al., 2013; Ye et al., 2014). We here report findings of TRF2 modulation impact on skeletal muscle both in vivo and in vitro.

Skeletal muscle is a largely a post-mitotic tissue; only satellites cells (>10% of the tissue) undergo replication and are thus subjected to telomere shortening. Therefore, it is expected that telomere length is not affected during muscle aging. Recently, telomeres and associated proteins have been implicated both in a muscular disorders with late onset (e.g: FSHD) and in muscle gene regulation (Robin et al., 2014; Robin et al., 2015). From our preliminary observations, we are reporting an unprecedented organization of telomere and TRF2 in post-synaptic nuclei. Unlike other cells from mice muscle fibers (i.e., Satellite, motoneuron, Schawnn cells), post-synaptic nuclei (located just under the neuromuscular junction) adopt a surprising telomere organization where telomeres and TRF2 are regrouped into limited clusters as opposed to the traditional mutli-foci pattern.

Using shRNA both in vivo (electroporated mice muscle) and in vitro (human myoblasts/myotubes) against TRF2, we observe a striking effect of this shelterin protein on the expression of genes implicated in autophagy, atrophy and neuromuscular junction stability in a DDR-independent manner.

Altogether, these results point to an important reorganization of telomere conformation and TRF2 in myonuclei, revealing an implication of TRF2 in myogenesis (e.g., myotubes formation) and muscle homeostasis.

Telomeres, Autophagie, Neuromuscular Junction

Homeostasis in the adult muscle- #2540

P14- 213- From voltage sensing to gene expression in the control of muscle mass homeostasis

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Muscle mass and fiber size undergo to rapid and significant changes according to environmental and pathological conditions. Electrical activity, evoked at neuromuscular junction, is decoded by the muscle voltage sensor, the L-type calcium channel Ca(V)a1s. Alterations in the pattern of nerve-evoked electrical activity convey in a modulation of the signal, due to modification in the gene expression. This excitation-transcription (E-T) coupling is crucial for plastic adaptation and compensation to mechanical stress and for isotypic determination of muscle fibers. However, it is still debated how important is the contribution of neurotrophic factors versus myogenic factors in the maintenance of muscle mass and function. Tacking advantage of both the DCa(V)a1s mouse model and of the denervation model of the hind limb by sciatic nerve resection, we are characterizing the intrinsic muscle ability to counteract the loss of mass. DCa(V)a1s muscles undergo atrophy (Piétri-Rouxel et al. 2010) and we observed that this muscle mass loss is counteracted by a compensatory response which involves the same pathway activated after muscle denervation, including Akt/mTor pathway, decreased Acv2BR and increased BMP14 levels. These evidences suggest that the activation/expression of the voltage sensor is the main responsible for muscle mass maintenance.

Studying the molecular pathway driving compensatory response, we focused on the voltage sensor complex component Ca(V)b1a, a subunit essential for the voltage sensing function of Ca(V)a1s. We found, for the first time, a drastic increase of Ca(V)b1a in muscles after denervation. To understand the role of the increased Ca(V)b1a expression during denervation atrophy, we selectively knocked down the protein in vivo and in adult muscle by AAV2/1-sh Ca(V)b1a. We found that the lack of Ca(V)b1a induces muscle atrophy and weakness in healthy muscle and exacerbates muscle mass loss after denervation, suggesting that Ca(V)b1a as a the key molecule essential to modulate the compensatory response to atrophy.

These data shed light on a new important mechanism regulating the adult muscle mass. This will be also studied in pathophysiological conditions such as age-related sarcopenia and congenital myopathies, and represent possible therapeutic target for highly threatening neuromuscular diseases

Ca(V)alpha1S, Ca(V)beta1a, atrophy, denervation, compensation,

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Homeostasis in the adult muscle- #2541

P14- 214- Rev-erb-? exacerbates endoplasmic reticulum stress-induced apoptosis in mouse skeletal muscle

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Background: Decreased muscle mass has been described in the context of obesity. Among the proposed mechanisms, endoplasmic reticulum (ER) stress that triggers unfolded protein response UPR, has been evoked as skeletal muscle apoptosis inducer. Interestingly, recent reports identified that UPR-related gene are differentially expressed around the clock. Intracellular clock machinery involves several proteins including the nuclear receptor Rev-erb-?. However, its role on skeletal muscle UPR and apoptosis has never been explored.

Aims: We hypothesize that Rev-erb-?, by modulating UPR, affects ER stress-induced apoptosis, and ultimately obesity-related skeletal muscle mass loss.

Methods: We first treated C2C12 myoblasts over-expressing Rev-erb-? with tunicamycin, a glycosylation inhibitor triggering UPR, in order to determine whether Rev-erb-? modulates UPR and apoptosis signaling. Then, we evaluated the effects of tunicamycin injection in skeletal muscle of wild-type and Rev-erb-? knockout mice. Finally, we tested whether Rev-erb-? modulates obesity-induced muscle mass.

Results: In response to tunicamycin, Rev-erb-? over-expression in C2C12 cells caused higher UPR-related gene expression (Grp78, Gadd34, Atf4, Atf6, Xbp1s, Chop) and IRE-1 phosphorylation. This was associated with greater tunicamycin-induced caspase-12 cleavage, caspase-3 activity and nuclear apoptosis. Inversely, tunicamycin-triggered UPR and apoptosis activation was diminished in gastrocnemius from Rev-erb-? knockout mice compared to wild-type animals. Finally, high-fat diet-induced obesity increased UPR-related gene expression and was associated with reduced gastrocnemius and quadriceps mass in wild-type mice, contrary to Rev-erb-? knockout littermates.

Conclusion: Rev-erb-? potentiated UPR-induced apoptosis in skeletal muscle. Rev-erb-? could represent a new therapeutic target to modulate obesity-induced muscle mass loss.

Rev-erb-?, endoplasmic reticulum stress, apoptosis, skeletal muscle

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Homeostasis in the adult muscle- #2575

P14- 215- Monitoring changes in sodium content and biodistribution by 23Na NMR spectroscopy in skeletal muscle tissue

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The sodium ion is involved in a vast number of functions at the cellular level. Changes in the intracellular concentration of sodium or in the volume fraction are associated with disorders that alter cell function/integrity or that cause metabolic changes. In order to discriminate the intra- from the extracellular Na+ signal two NMR methods have been previously proposed: inversion-recovery methods and triple quantum filtration (TQF). Here, we evaluated the sensitivity of different parameters (FID signal, TQF signal, TQF/FID ratio, T1 value, short T2* fraction) to assess the intracellular sodium content as well as its distribution with acquisition times compatible with clinical investigation.

Healthy volunteers were scanned on a 3T scanner. Data were acquired on the calf, under different vascular filling conditions expected to modify the extracellular volume exclusively (vascular draining, vascular filling, normal conditions). Total sodium content and short T2* fraction were derived from an FID sequence. Slowly tumbling Na+ signal was estimated by TQF. T1 relaxation times were quantified with an inversion-recovery sequence.

Significant variations of FID signals, TQF signals, TQF/FID ratios, T1 values and short T2* fractions were observed between the 3 conditions. FID signals and T1 values were increased with vascular filling and decreased with vascular draining as compared with control conditions while the opposite trend was observed for short T2* fraction, TQF/FID ratio as well as TQF signal. The TQF/FID ratio was the most robust and sensitive index to discriminate between the three conditions. There were significant correlations between T1 and TQF/FID ratio and between short T2* fraction and TQF/FID ratio.

In conclusion, by using 23Na NMR spectroscopy, indices sensitive to changes in sodium biodistribution and interaction with macromolecules can be acquired in human skeletal muscles with acquisition times compatible with investigation of patients in a clinical research setting (>15min).

sodium NMR; skeletal muscle; biodistribution

Homeostasis in the adult muscle- #2919

P14- 216- Synemin acts as a regulator of signalling molecules in skeletal muscle hypertrophy

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Synemin, a type IV intermediate filament (IF) protein, forms a bridge between IFs and cellular membrane. An A-kinase anchoring protein, it also provides temporal and spatial targeting of protein kinase A (PKA). However, little is known about its functional roles in either process. To better understand its functions in muscle tissue, we generated synemin-deficient (Synm-/-) mice. Synm-/- mice displayed normal development and fertility but had mild degeneration/regeneration of myofibres and defects in sarcolemma membranes. Following mechanical overload, Synm-/- mice muscles showed a higher hypertrophic capacity with increased maximal force and fatigue resistance than control mice. At the molecular level, increased remodelling capacity was accompanied by decreased myostatin and atrogin expression and increased follistatin expression. Further, the activity of muscle mass control molecules (PKA-RIIa, p70S6K, CREB) was increased in mutant mice. Finally, analysis of muscle satellite cell behavior suggested that the absence of synemin could affect the balance between self-renewal and differentiation of these cells. Taken together, our results show that synemin is necessary to maintain membrane integrity and regulates signalling molecules during muscle hypertrophy.

Desmin, muscle hypertrophy, intermediate filaments, skeletal muscle

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Homeostasis in the adult muscle- #2920

P14- 217- The absence of desmin results impaired adaptive response to mechanical overloading of skeletal muscle.

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The aim of this study was to examine the role of desmin on muscle performance gain and remodeling induced by muscle mechanical overloading (OVL), that mimics resistance training. The response to mechanical OVL in mice in which desmin is ablated (KO) was compared to that of wild-type mice (WT). In contrast to WT mice, we found that KO mice muscle do not increase absolute maximal force following mechanical overload ($p > 0.05$). It should be noted that the specific maximal force (force normalized to muscle weigth) was decreased by 1-month OVL in KO mice ($p > 0.05$) but it was preserved in WT. Concerning fatigue resistance, it was increased less after 1-month OVL in KO mice as compared to WT mice ($p > 0.05$). In contrast the impaired functional adaptive response of KO mice to mechanical overloading, muscle weight and the fiber number per cross-section similarly increased in both genotypes after 1-month OVL ($p > 0.05$). The MHC-2b to MHC-2a fiber type transition in response to 1-month OVL was slightly reduced in KO mice as compared to WT mice ($p>0.05$). In addition, to elucidate the molecular mechanisms implicated in increased muscle adaptive response of KO mice following OVL, we examined the mRNAs involved in muscle growth, myogenesis, inflammation and oxdative energetic metabolism by quantitative real-time PCR. Analyses were performed on muscle samples 7 days after OVL to analyse changes occurring during the early phase of muscle remodelling. Finally, analysis of muscle satellite cell behavior suggested that the absence of desmin could affect the balance between self-renewal and differentiation of these cells following OVL. Taken together, our results show that desmin is required for a complete response to mechanical OVL in mice.

Desmin, muscle hypertrophy, intermediate filaments, skeletal muscle

Homeostasis in the adult muscle- #3215

P14- 218- Specific protein changes contribute to the differential muscle mass loss during ageing

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In the skeletal muscle, the ageing process is characterized by a loss of muscle mass and strength, coupled with a decline of mitochondrial function and a decrease of satellite cells. The decline of repair capacity and muscle mass lead to decreased physical activity, increased frailty, and ultimately loss of independent living of the elderly population. Hindlimbs and forelimbs are differently affected by sarcopenia, being more pronounced in hindlimb than in forelimb muscles, both in humans and animal models and the molecular players are far from being clarified. On the other hand, ethical reasons hamper further assessments of molecular changes in humans, particularly the comparison of different muscles from the same subject, making the use of animal models mandatory.

Utilizing light and electron microscopy, MyHC isoform distribution, proteomic analysis by 2D-DIGE, MALDI-ToF MS and quantitative immunoblotting, this study analyzed the protein levels and the nuclear localization of specific molecules, which can contribute to a preferential muscle loss.

Our results identify the molecular changes in the hindlimb (gastrocnemius) and forelimb (triceps) muscles during ageing in rats (3- and 22-month-old). Specifically, the oxidative metabolism contributes to the tissue homeostasis in the triceps, whereas respiratory chain disruption and oxidative-stress-induced damage imbalance the homeostasis in the gastrocnemius muscle. High levels of Dlat and Atp5a1 are detected in the triceps and the gastrocnemius, respectively. Interestingly, in the triceps, both molecules are increased in the nucleus in aged rats and are associated to an increased protein acetylation and myoglobin availability. Furthermore, autophagy is retained in the triceps whereas an enhanced fusion, decrement of mitophagy and of regenerative potential is observed in the aged gastrocnemius muscle.

By the present study we can provide better insight into physiological muscle waste but also contribute to the comprehension of pathophysiological mechanisms of some neuromuscular disorders, characterized by a preferential onset targeting upper or lower extremities, e.g. facio-scapulo-humeral dystrophy (FSHD) or sporadic inclusion body myositis (sIBM).

intermediate metabolism, muscle ageing, 2D-DIGE, muscle proteome, mass spectrometry

P15- Inflammatory myopathies /- N° 219 to N° 237

Inflammatory myopathies- #2298

P15- 219- Inclusion body myositis with granuloma formation in muscle tissue

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Inclusion body myositis is a form of inflammatory myopathy. We identified 4 cases of inclusion body myositis showing granuloma formation in muscle tissue and aimed to assess the features of this atypical form of the inclusion body myositis.

We retrospectively reviewed consecutive patients who satisfied European Neuromuscular Centre IBM Research Diagnostic Criteria 2011. Then, we assessed clinical profiles and pathological findings in patients with inclusion body myositis with granuloma and compared these findings with those of typical inclusion body myositis without granuloma.