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 weight) 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 oxidative 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

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 isofrom 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.
We identified 15 patients with inclusion body myositis. Four patients showed granuloma formation in muscle tissue in addition to typical pathological features of inclusion body myositis. Granulomas comprised a mixture of inflammatory cells, such as macrophages, epithelioid histiocytic cells, and lymphocytes. One patient was found to have mediastinal granulomatous lymphadenopathy; however, the evidence in other patients was insufficient for a diagnosis of systemic sarcoidosis. There were no significant differences between groups with and without granuloma regarding clinical manifestations, laboratory findings, response to immunomodulating therapies, or myopathic profiles.

We established a new form of inclusion body myositis showing granuloma formation in muscle tissue. Inclusion body myositis and granuloma formation could have identical pathomechanisms concerning dysregulation of autophagy.

inclusion body myositis, granuloma, rimmed vacuole, autophagy

Inflammatory myopathies- #2527

P15- 220- IMMUNE MEDIATED NECROTIZING MYOPATHIES AND INTRAVENOUS IMMUNOGLOBULIN
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Necrotizing myopathies are divided into immune mediated and nonimmune mediated. The immune mediated form (IMNM) is associated with anti-signal recognition particle antibody, connective tissue diseases, cancer, post-statin exposure with 3-hydroxy-3-methylglutaryl-coenzyme A antibodies (HMGCoA) and viral infections including HIV and C virus hepatitis. Here we present our experience in two cases of IMNM associated with statin exposure successfully treated with intravenous immunoglobulins (IV Ig) after failure of standard treatment. The first case is a 62 years old woman who presented with proximal muscle weakness as initial symptom. She had history of statin exposure and the HMGCoA antibodies were positive. A muscle biopsy was performed with the unequivocal diagnosis of IMNM. Corticosteroids as well as immunopressants such as azathioprine and cyclosporine were the first therapeutic options without improvement during the first three months after disease onset. IV Ig was then started achieving remission. The second case is a 73 years old woman with history of statin exposure. She presented with subacute generalized muscle weakness and severe dysphagia. Muscle MRI showed symmetric edema in deltoid and quadriceps muscles. The diagnosis of IMNM was made after muscle biopsy examination (fig. 1). Because no response to corticosteroids and azathioprine was noted, IV Ig was started. Both the weakness and dysphagia gradually improve. In this case IV Ig was started as a emergency treatment due to the severity of the clinical presentation. IV Ig is still indicated as maintenance therapy, several months after its introduction.

Inflammatory myopathies- #2559

P15- 221- Muscle ischemia is associated with antiNXP2 autoantibodies in Juvenile dermatomyositis.
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Figure 1 (patient number 2). A) Necrotic muscle fibers with active phagocytosis (hematoxylin-eosin). B) Necrotic muscle fibers showing abnormal sarcolemmal expression of MHC class 1 antigens. C) Necrotic muscle fibers show increased sarcolemmal expression of membrane attack complex (C5-b9 MAC). Abnormal (increased) expression in perimysial vessels is also noted.
Anti-NXP2 antibodies were identified in 5/12 of JDM patients. Patients with NXP2 auto-antibodies (NXP2 + group) as compared to those without NXP2 auto-antibodies (NXP2- group) exhibited more severe clinical presentation including vasculopathy-related features (limb subcutaneous edema, gastrointestinal involvement) leading to more aggressive treatment (plasmapheresis and immunoadsorption). Regarding the histological features, NXP2+ group compared to NXP2- group displayed more frequent ischemic involvement and adapt therapeutic strategy.

We retrospectively assessed clinical, biological and histological findings from 12 consecutive JDM patients diagnosed from June 2013 to January 2015 in both Pediatric rheumatology and dermatology referral centers. Systematic auto-antibodies screening (Mi2, MDA5, TIF1-gamma, NXP2, SAE, Ro52, Jo1, PL7, PL12, EJ, SRP, Ku, PM-Scl, Scl70,) and myopathological study of deltoid muscle biopsy (including immunohistochemistry for endothelial cells (CD31/PECAM), regenerating myofibers (CD56/NCAM) macrophages (CD68), T cells (CD3), B cells (CD20), anti-human major histocompatibility complex (MHC) class I (HLA-ABC), class II (HLA-DR), and C5b-9/MAC) were performed in all patients. All biopsies were reviewed using the recently validated score tool for muscle biopsy evaluation in patients with JDM (Varsani et al., 2015).

Anti-NXP2 antibodies were identified in 5/12 of JDM patients. Patients with NXP2 auto-antibodies (NXP2+ group) as compared to those without NXP2 auto-antibodies (NXP2- group) exhibited more severe clinical presentation including vasculopathy-related features (limb subcutaneous edema, gastrointestinal involvement) leading to more aggressive treatment (plasmapheresis and immunoadsorption). Regarding the histological features, NXP2+ group compared to NXP2- group displayed more frequent myofibers with ischemic punch-out vacuoles (in 4/5 vs 5/7) , microinfarcts (in 5/5 vs 4/7) and capillary dropout (in 4/5 vs 1/7) according to JDM score tool. None of the patient NXP2+ developed calcinosis.

These results suggested that NXP2+ auto-antibodies in JDM may be associated with a distinct clinical and histological ischemic-related phenotype. They don't confirmed their association with calcinosis.

In conclusion, positive detection of anti-NXP2 auto-antibodies in JDM may contribute to identify patients with more severe ischemic involvement and adapt therapeutic strategy.

**Juvenile Dermatomyositis, ischemic myopathy, muscle infarction**

**Inflammatory myopathies- #2736**

**P15-222- IFN? induced HLA-DR expression by human myogenic cells is associated with differentiation inhibition**

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Myofiber HLA-DR expression in human muscle diseases is regarded as witnessing IFNg-driven inflammation. Most of the in vitro studies investigating the action of IFNg on myogenic cells have been conducted on murine C2C12 cells, with the limitations due to derives inherent of a cell line. Here we describe the effects of IFNg on primary cultures of human myogenic cells, during the proliferative phase and after differentiation into myotubes. We monitored the expression of the receptors IFNGR1 and IFNGR2, as well as the expression of the genes involved in the IFNg pathway (CIITA, HLA-DM and HLA-DR), and finally the expression of the genes associated with stemness (Pax7), commitment (MyoD) and differentiation process (Myogenin).

Under IFNg treatment, sarcolemmal expression of IFNGR1 appeared increased, while the IFNGR2 expression remained constant. RT-qPCR showed marked increase of the expression of CIITA, HLA-DM and HLA-DR following IFNg exposure in proliferating cells (x3.67 104 , x8.1 103 , and x3.45 104 , respectively) and at differentiated stage (x2.66 103 , x1.1 103 , and x2.97 103 , respectively). The expression of Myogenin was downregulated during the differentiation process at undifferentiated (x0.014) and differentiated (x0.81) stages while those of Pax7 and MyoD seemed unchanged after IFNg treatment.

We conclude that IFNg is a potent inducer of HLA-DR expression by human myogenic cells, in association with the repression of myogenic differentiation. These results enlighten the role of IFNg in human pathology.

**IFN?, HLA-DR, human myogenic cells**

**Inflammatory myopathies- #2794**

**P15-223- Effects of anti-signal recognition particle (SRP) and anti-Hydroxyméthylglutaryl-CoA reductase (HMGCR) auto-antibodies on muscle cells**

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Necrotizing myopathies (NM) might be acquired auto-immune muscle diseases, in which muscle biopsy demonstrates marked muscle necrosis with regeneration, little or absence of inflammatory infiltrates and a particular pattern of complement C5b-9 deposition on muscle fibers. NM can be seropositive for some auto-antibodies (aAbs) such as anti-SRP as well as anti-HMGCR. The titer of these aAbs is correlated with the creatine kinase levels, but their role remains unclear. In the current study, we investigated the effect of the anti-SRP and anti-HMGCR aAbs on in vitro primary human myoblast/myotube cultures. To study the effect of the auto- Abs on muscle cells, confluent myoblasts and 3 day myotubes were incubated with anti-SRP or anti-HMGCR positive human IgG for 72 hours or with human polyclonal immunoglobulins (IVIg) as a control.

We demonstrate that the addition of the aAbs onto differentiated myotubes leads to atrophy, as measured by a reduction in the size of myotubes (anti-SRP 66.5±2.6 µm², anti-HMGCR 66.5±4.8 µm² vs control 147.8±5.4 µm², p>0.001). The expression of atrophic genes such as Atrogin and Murf-1 was measured by qPCR, the culture with anti-SRP Abs shows an increase of Atrogin expression but the anti-HMGCR shows an increase of Murf1 compared to the control.

Furthermore, addition of the aAbs to confluent myoblasts significantly reduced the capacity of myoblasts to form myotubes (anti-SRP 44.2±7.1 µm², anti-HMGCR 53.6±7.7 µm² vs control 147.8±5.4 µm², p>0.001). To understand the pathway leading to this phenomenon many hypotheses were explored such as the diminution in the number of cells, the inhibition of the differentiation program or the decrease of the fusion capacity. Our results demonstrate a problem in the secondary fusion correlated with a decrease in the expression of the IL4 cytokines in the presence of anti-SRP or anti-HMGCR. These findings suggest that anti-SRP and anti-HMGCR aAbs have a pathogenic effect on muscle cells in vitro by both inhibiting cell fusion and triggering atrophy on fully differentiated myotubes.

**myoblast, myotube, auto-antibodies, atrophy, differentiation, fusion.**

**Inflammatory myopathies- #2813**

**P15- 224- Behcet disease and focal myositis association, case reports and literature review.**

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Focal Myositis (FM) is characterized by inflammation localized in a skeletal muscle. Morphological investigation underscore hyperintense focal image in FAT SAT T2 MRI sequences. Muscle biopsy shows inflammatory infiltrates, predominantly composed of T cells (mainly CD4+), diffuse and faint membranous expression of HLA-I, fibers diameters irregularity, necrotic and regenerative fibers and fibrosis. Pertaining nosology and pathogenesis are still unclear. Systemic disease and FM association are rarely reported. Behcet's Disease is a vasculitis involving vessels of variable sizes (Variable Vessel Vasculitis), with a clinical pattern affecting multiple organs, most notably skin or mucosal condition, joint, neurological or vascular involvement. We report 3 cases of Behcet Disease who presented secondaryarily FM. In this specific association, FM seems to differ from the usual FM pattern regarding some features. In particular, in our cases, as in literature's data, the average age of onset is younger, the clinical picture seems to be more severe, including systemic symptoms (fever, asthenia, focal intense pain), and relapses appear to be more frequently observed. Interestingly, other differences are identified regarding the histological pattern, notably, presence of leucocytoclastic and necrotizing vasculitis in the muscular biopsy.

**Focal Myositis, Behcet Disease, Necrotizing vasculitis**

**Inflammatory myopathies- #2816**

**P15-225- Serum immunological markers in a cohort of 101 patients with Inclusion Body Myositis.**

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Introduction:

Inclusion Body Myositis (IBM) is the most frequent myositis among the population over 50 years of age. Its pathogenesis conjugates inflammation, immunity and neuro-degeneration processes. The objective of the work was to evaluate the serum immune anomalies in a large cohort of IBM patients.

Methods:

Starting from the French database ?Idiopathic inflammatory myopathies?, (960 patients), all the eligible IBM patients (n=228), considering Benveniste et al IBM criteria (1) were sorted out. From this cohort, patients who had immunological investigations were selected (n=101).

Results:

The cohort consisted of 51 men, 50 women, with an average age of 71.2 years old. Fifty nine patients (58%) had at least once positive anti nuclear antibody (ANA). ANA titers distribution was: 1/80 = 42%, 1/160 =26%, 1/320 =19%, 1/640 3%, and ?1/1280
Among 228 eligible IBM patients (1), 101 had immunological investigations. Anti SSA-SSB seropositive patients were compared

Methods

Inflammation and neuro-degeneration processes. Our objective was to investigate IBM and anti SSA-SSB antibody association.

Inclusion Body Myositis (IBM) is the most frequent myositis among the population over 50. Its pathogenesis conjugates immuno-

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explore autoimmunity in IBM. Further longitudinal studies are needed to show any impact for the treatment response.

Though no major differences were found between SSA/SSB+ and the control groups, this work highlights the necessity to

autoantibodies and 10 patients were diagnosed as SS. For this sub-group, anti-nuclear antibody were more commonly found.

While prevalence of antibodies anti-SSA/SSB was 4.9% in the general population, 21% of our IBM cohort presented such

Conclusion

Serum autoimmune stigmata were found in approximately 2/3 of this cohort. This proportion is more important than expected in

the general population over 70 years old (19.2%) (2). As previously reported, Anti-cN1A positivity was found in more than half of

the patients. In particular, we observed a higher frequency of monoclonal gammapathy in IBM patient compare to the general

population of the same age group (24% vs 4%).

This study thus suggests an immunological involvement in IBM pathogenesis, and outlines the need to investigate consistently

immune status in this particular disease.

Inclusion Body Myositis, immunological markers, gammapathy, retrospective study

Inflammatory myopathies- #2817

P15-226- Presence of anti SSA-SSB antibody in Inclusion Body Myositis: a case-control study on 42 patients.

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Introduction

Inclusion Body Myositis (IBM) is the most frequent myositis among the population over 50. Its pathogenesis conjugates immuno-

inflammation and neuro-degeneration processes. Our objective was to investigate IBM and anti SSA-SSB antibody association
to compare epidemiologic, clinic, morphologic, and immunologic data of this association.

Methods

Among 228 eligible IBM patients (1), 101 had immunological investigations. Anti SSA-SSB seropositive patients were compared
with an appropriate age and gender matched set of 1/1 seronegative IBM. Demographic, clinical, immuno-biological and
radiological data were compared using appropriate tests.

Results:

Twenty-one IBM patients (21%) were anti-SSA/SSB antibody seropositive. Twenty patients had anti-SSA52 (95%) apportioned
as follows: anti-SSA52 isolated (28%), associated with SSA60 (67%), SSA60 isolated (5%). Anti-SSB were found in 11 patients
(52%).

Xerophtalmia was reported for 13/16 patients (81%). Salivary gland biopsy was positive (Chisholm grade III-IV) in 7/10 cases
(70%). All together and according to the International classification criteria, 10 (50%) patients were diagnosed as
primary/secondary Sjögren Syndrome (SS).

Comparison of anti-SSA/SSB+ with control-seronegative groups revealed no significant differences for lymphopenia (50% vs
38%) nor Creatine Kinase levels (645 vs 608 UI/L). Plasma protein electrophoresis abnormalities prevalence was high: 84% vs
50%, p=0.08), with gammapathy in 15 SSA/SSB+ patients.

Furthermore, 86% of the SSA/SSB+ patients had anti-nuclear antibody levels ?1/320, compared with 12% of the seronegative
IBM (p>0.001). Anti-cN1A antibodies were detected in both groups with no significant difference (83.3% vs 100%, respectively,
which is higher than the average of 57% in the whole cohort). Independently from the groups, numerous IBM patients presented
anomalies consistent with SS: dysthyroidia (38 versus 29%) and mild lung abnormalities on the thoracic CT-scan, with no
specific pattern.

Conclusion

While prevalence of antibodies anti-SSA/SSB was 4,9 % in the general population, 21% of our IBM cohort presented such
autoantibodies and 10 patients were diagnosed as SS. For this sub-group, anti-nuclear antibody were more commonly found.
Though no major differences were found between SSA/SSB+ and the control groups, this work highlights the necessity to
explore autoimmunity in IBM. Further longitudinal studies are needed to show any impact for the treatment response.

Inclusion Body Myositis, Anti SSA-SSB antibody, Sjögren Syndrome

Inflammatory myopathies- #2853

P15-227- Role of hypoxia in innate immunity activation in dermatomyositis

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Classically, it is accepted that the pathogenesis of DM involves loss of intramuscular capillaries as a consequence of an
autoimmune attack to as yet unidentified target antigens on endothelial cells. This leads to reduced levels of oxygen and
nutrients that promote muscle fiber atrophy, especially in the perifascicular areas. It has been reported that type I interferons
(IFN-I) have an important role in DM. We previously reported that the retinoid acid-inducible gene 1 (RIG-I), a receptor of innate
immunity and an IFN-inducible gene, is expressed in perifascicular areas in muscle biopsies of patients with DM and triggers IFN-I response in human myotubes. The aim of the study was to demonstrate that hypoxia has an effect on innate immunity pathways in dermatomyositis. We analyzed frozen sections from muscle biopsies, human muscle primary cultures and HEK293 cells grown in normoxia and hypoxia by immunohistochemistry, qPCR, western-blot, cloning and by luciferase assays.

We observed that HIF1α, a key protein that regulates hypoxia responses, is expressed in perifascicular areas in DM biopsies. In vitro, hypoxia induces the expression of RIG-I in human myotubes. Accordingly, cloning and luciferase assays demonstrates that RIG-I is an hypoxia-inducible gene. Interestingly, the overexpression of RIG-I induces the phosphorylation of IRF3 and IFN transcription without an exogenous agonist.

We also observed in the perifascicular areas of muscle biopsies of patients with DM increased accumulation of PAS+ material. We also observed in the perifascicular areas of muscle biopsies of patients with DM increased accumulation of PAS+ material. We also observed in the perifascicular areas of muscle biopsies of patients with DM increased accumulation of PAS+ material.

In conclusion, myofiber HLA-DR expression is mainly associated with overlap myositis (perifascicular) and IBM (patchy), and absent in DM.

\[ \text{HLA-DR, inflammatory myopathy, inclusion body myositis} \]

\[ \text{neuromyotonia, myokymia, inflammatory myopathy, polymyositis} \]
Background. Macrophagic myofasciitis (MMF) is characterized by specific muscle lesions assessing abnormal long-term persistence of aluminium hydroxide within macrophages at the site of previous immunization. Affected patients mainly present with diffuse arthromyalgias, chronic fatigue, and cognitive dysfunction.

Patients & Methods. 100 consecutive MMF patients (mean age, 45.9 ± 11.8 y; women, 74%) followed in GNMH Reference Center for Neuromuscular Diseases underwent a comprehensive battery of neuropsychological tests and 18F-fluorodeoxyglucose (18F-FDG) PET brain imaging. Images were analyzed using statistical parametric mapping (SPM12). Using ANCOVA analyses, all FDG PET brain images of MMF patients were compared to normal reference samples from 44 healthy subjects similar for age (p=0.87) and gender (p=0.88) with the whole-group (mean age, 45.4 ± 16 y; women, 73%). All results were collected at a P-value>0.005 at the voxel level, for clusters k > 200 voxels (corrected for cluster volume) with adjustment for age and sex. The neuropsychological analysis identified four categories of patients with MMF: patients with: (i) no significant cognitive impairment (n=42); (ii) frontal sub-cortical (FSC) dysfunction (n=29); (iii) Papezian dysfunction (n=22); and (iv) callosal disconnection (n=7).

Results. In comparison to healthy subjects, ANCOVA analysis of whole-group of patients with MMF exhibited a significant decreased uptake of FDG (p=0.001) in an atypical and symmetrical pattern involving occipital lobes, temporal lobes, limbic system, cerebellum and frontoparietal cortices. The MMF group with FSC dysfunction exhibited the larger extent of involved area (35223 voxels vs. 13680 voxels for the group with Papezian dysfunction and 5453 voxels in patients without cognitive impairment). No significant change was observed in the group with callosal disconnection.

Conclusions. Our study identified a cerebral glucose metabolism biomarker of patients with long-lasting aluminium hydroxide-induced MMF. The pattern appeared mostly marked in MMF patients with FSC dysfunction.

macrophagic myofasciitis, aluminum, PET, macrophages
Sporadic Inclusion Body Myositis (sIBM) is the most common acquired skeletal myopathy in individuals above the age of 50 years. Its development is multifactorial involving genetic predisposition, environmental stress and ageing factors. Muscle morphology reveals a strong inflammatory/immune process, degenerative features and mitochondrial (mt) alterations leading to muscle fiber atrophy/cell death. Although the morphological alterations are respectively well characterized, the time sequence of the molecular events is not known.

Methods
We used microarrays to study the whole expression pattern of vastus lateralis muscle specimens from 27 male subjects, 17 from sIBM patients and 10 from adult control subjects; Gene Ontology Functional Enrichment and KEGG Pathway Analysis for Differentially Expressed Genes were extensively explored.

Results
In sIBM muscle, a great number of genes related to innate immunity and humoral/cell-mediated responses were concerned as expected. We focused on the innate immune response, which represents the first step of the immune process. The pattern-recognition receptors (PRRs) of the innate immune system including the Toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and the nucleotide-binding, oligomerization domain (NOD)-like receptors (NLRs) were consequently up-regulated. NLRs signaling pathways seemed the most striking. Indeed the majority of the genes belonged to that pathway were upregulated; the genes concerned specific inflammasome components (NLRs pathway), signal transducer of the NF-kB pathway, and proinflammatory cytokines or chemokines. On contrary, NLRC4 (IPAF) expression did not differ between sIBM and control subjects.

Discussion / Conclusion
We observed for the first time to our knowledge, activation of the NLRs signaling pathways in sIBM muscle. NLRs dysregulation has been recently implicated in various diseases such as autoinflammatory disorders, metabolopathies and neurodegenerative diseases. Interestingly this pathway gives also the opportunity to link distinctive morphological alterations described in sIBM muscle through interactions with inflammasomes such as beta-Amyloid, oxidized mt DNA, ROS production, and lysosomal damage. Complement immunohistochemical validations are currently done to correlate the status of the innate immune response with others hallmarks of the disease such as degenerative changes and mt dysfunction.

Inflammatory myopathies- #2976

P15-233- ACTIVATED DENDRITIC CELLS MODULATE HUMAN MYOBLAST PROLIFERATION AND DIFFERENTIATION
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Inflammatory myopathies (IM) are diseases characterized by clinical symptoms such as progressive weakness and loss of skeletal muscle strength and inflammatory infiltrations. Inflammatory infiltrations generates muscle tissue damage and exacerbates the progression of the disease and muscle weakness. The muscle histopathology of IM is characterized by the presence of inflammatory cells such as T lymphocytes, macrophages and dendritic cells (DC). In several IM, DC are found surrounding or even invading necrotic and non-necrotic muscle fibers indicating a possible role of DC's in the progression of degenerative muscle diseases. However, the interaction between DC and myoblasts (MB), cells that are responsible for muscle regeneration, has not been clearly determined. Therefore, the aim of this study was to determine whether there is an interaction between DC and MB and if this interaction drives morphological and functional changes in MB.

In order to answer this question, we designed a co-culture assay of MB plus DC, both isolated from healthy donors. In order to study the effect of immature DC (iDC) and activated DC (actDC), the co-culture was incubated with medium or LPS, respectively. We observed by fluorescent, confocal and electron microscopy that actDC were tightly adhered to MB during both proliferation and differentiation. We observed that DC induced an increase in MB proliferation analyzed by BrdU incorporation. We observed that this effect was more pronounced with actDC. During differentiation in these co-culture conditions we observed a decrease in myotube formation, and a decrease in MyoD and MyoG expression. Furthermore, during differentiation in the presence of DC supernatants there was also a mild decrease in the same parameters, thus suggesting the involvement of secreted factors. Again, the aforementioned differences were more pronounced in the actDC co-culture. Regarding secreted cytokines, we observed an increase in the secretion of IL-10 and IL-13 during both differentiation and proliferation. Finally, there was an increased HLA-ABC and HLA-DR expression in the MB after co-culture, specially with actDC.

In conclusion, our data suggests that actDC could contribute to the clinical evolution of IM since it alters MB profile by increasing proliferation and decreasing myotube formation.
Myoblast, myotube, dendritic cell, inflammatory myopathies

Inflammatory myopathies- #3009

**P15- 234- Anti-mitochondrial-M2 antibodies associated myositis.**

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Anti-mitochondrial-M2 antibodies (AMMAs) are observed in 90% of primary biliary cirrhosis (PBC) but were recently reported associated with isolated myositis with frequent cardiac involvement and atrophic phenotype on histology. To determine the importance of such antibodies we conducted a retrospective analysis in the cohort of inflammatory myopathies (IM) in La Pitié Salpêtrière Hospital.

Among 960 patients with IM according to Hoogendijk criteria, 9 patients (7 females) presented AMMAs on indirect immunofluorescence assay with diagnostic of polymyositis (PM; n:5), necrotizing autoimmune myopathies (NAIM; n:2), anti-synthetase syndrome (n:1) and aspecific myositis (n:1). No history of muscular dystrophy was reported. Muscle weakness was observed in 8/9 at diagnosis, 7/8 had walking limitation, 3/8 had swallowing disorders. Two patients had inflammatory hypersignal on heath MRI, ventricular function decreased in one. Mean creatine phosphokinase level was 9015U/l (132- 51596). T2 hypersignals were observed in 6 among the 7 patients with available MRI. Among PMs, one patient had associated lupus and Sjogren syndrome, another patient had isolated Sjogren syndrome. No cancer was observed except one hepatocarcinoma that developed in the course of hepatitis C associated cirrhosis in a NAIM patient. Extra-muscular disorders were Non Specific Interstitial Pneumonia (n:2), PBC (n:3), arthralgia (n:5). All the biopsies showed atrophic fibers with irregular diameter. Eight among 9 showed necrotic fibers and CMH-1 expression. Plasma membrane proteins staining was normal. AMMAs were the only antibodies in 1 patient, associated to anti-Gp210 or Sp100 in 3 patients of whom 2 had PBC.

A treatment was initiated in the 8 patients with muscle weakness: all received corticosteroids, 5 methotrexate, 4 intravenous Immunoglobulin, 2 cyclophosphamide, 1 rituximab, 1 mycophenolate mofetil, 4 had plasmatic exchanges. One death occurred (patient with hepatocarcinoma), 2 patients benefited from a methotrexate-corticosteroid biotherapy whereas the others needed therapeutic intensification.

We thus confirm the existence of IM with AMMAs, frequently associated with PBC and often presented with a chronic and corticoresistant evolution.

**myositis, diagnostic, anti-mitochondrial antibodies**

Inflammatory myopathies- #3029

**P15- 235- Clinical epidemiology of idiopathic inflammatory myopathies: towards a classification based on myositis specific autoantibodies**

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The idiopathic inflammatory myopathies (myositis) are a group of autoimmune diseases, debilitating, rare (incidence: 5-10 cases/106, prevalence: 50-100 cases/106), complex and heterogeneous in their pathophysiology and prognosis. The emergence of new biomarkers, such as myositis specific autoantibodies (MSA) seems to define more homogeneous subgroups of patients.

**Patients&Methods:**

1) Myositis defined according to the reference classifications: Dermatomyositis (DM), Polymyositis (PM), Necrotizing Autoimmune Myopathies (NAM) by Hoogendijk & al in 2004, and Inclusion Bodies Myositis (IBM) with the Lloyd & al, 2014 criteria.
Importantly, an in depth comparison with the temporal differentiation processes in mouse and human primary satellite cells

cytokines (particularly CXCL9 and CXCL10) and skeletal muscle wasting in a pre-clinical model of COPD (PMID 25228925). In

omics dataset exposing C2C12's to a panel of inflammatory and hypoxic signals during the myogenic differentiation process.

order to further understand the link between inflammation and peripheral muscle dysfunction, we have developed a multi-level

Big Data analysis, hypothesis generation and subsequent validation. The approach we choose for the molecular characterisation is

represents the molecular and phenotypic characterisation to the response to cytokines and hypoxia, followed by bioinformatics

different in vitro treatments, we have come up with a set of testable hypotheses about which factors could be important in the

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2) Patients included during routine visit in our centre, who began their monitoring from 2003, year of availability of antibody

detection kits.

Observational, monocentric study.

Main objective: To study whether the presence of MSA is associated with characteristic phenotypes.

Statistical analysis: in Stata/IC 11.1. Student’s t test or non-parametric Mann-Whitney/ ANOVA tests (continuous variables) and

Chisq test or Fisher (categorical). Multivariate analysis cluster analysis and study survival (Kaplan-Meier/log-rank tests).

Preliminary results: 484 patients selected and the medical records of 239 patients reviewed (including 20 screening failures: 13

not myositis, 7 without MSA detected). On 219 patients, 140 women (64%) and 79 men (36%), we have 79 IBM (36%), 59 NAM

(27%), 35 DM (16%), 29 Anti-Synthetase Syndrome (ASS)(13.2%), 14 Overlap Polyomyositis (OP) (6.4%) and 3 pure PM

(1.4%).128 patients (58.5%) have MSA: 36 IBM (45.5%), 47 NAM (79.6%), 16 DM (46%; 1 double positive anti-Mi2/anti-TIF1?), 29

ASS (100%) and DPM/Op. Among IBM, there were more men (p=0.015), and less axial deficit (p=0.048) in the groups of

those with anti-cN1A compared to the seronegative. NAM present significant extramuscular differences: Patients with anti-SRP

and seronegative have more pulmonary damage (p=0.047) with diffuse interstitial pneumonia (p=0.0001), heart damage

(p=0.04), arthralgia (p=0.015), Raynaud (p=0.025), presence of myositis associated autoAb (p=0.003) and connective disease

(p=0.028) compared to patient with anti-HMGCR. However patients with anti-HMGCR present more cancer than patients with

anti-SRP and seronegative (p=0.010).

The next step is cluster analysis.

This reclassification could help to find an optimal therapeutical regimen by myositis, and /or to clarify their pathophysiology, and

/or to identify judgments criteria adapted for therapeutic trials

Inflammatory myopathies, autoantibodies, classification

Inflammatory myopathies- #3041

P15- 236- A data driven approach to understand the impact of inflammation and hypoxia on skeletal muscle biology

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A characteristic feature of aged humans and other mammals is the progressive loss of skeletal muscle function and mass that is

known as sarcopenia. Moreover, loss of muscle mass and muscle dysfunctions occur in numerous diseases, such as cancer, chronic obstructive pulmonary disease (COPD), diabetes, HIV. Muscle-derived cytokines and growth factors (myokines) might contribute to skeletal muscle frailty by influencing metabolic homeostasis and systemic aging. In addition, reactive oxygen species activities in many tissues increase with age and there is evidence that increased ROS generation may be the underlying reason for several age-related pathologies. Therefore, it is known that numerous factors can influence loss of tissue regeneration ability and increased oxidative damage in ageing but our hypothesis is that cytokines and tissue hypoxia have the biggest impact. Using a system biology approach, in my group it has been already established a link between circulating cytokines (particularly CXCL9 and CXCL10) and skeletal muscle wasting in a pre-clinical model of COPD (PMID 25228925).

In order to further understand the link between inflammation and peripheral muscle dysfunction, we have developed a multi-level omics dataset exposing C2C12's to a panel of inflammatory and hypoxic signals during the myogenic differentiation process. Importantly, an in depth comparison with the temporal differentiation processes in mouse and human primary satellite cells confirms that the C2C12 cell line behaves in a very comparable manner at the transcriptional level. This novel dataset represents the molecular and phenotypic characterisation to the response to cytokines and hypoxia, followed by bioinformatics analysis, hypothesis generation and subsequent validation. The approach we choose for the molecular characterisation is genome-wide expression profiling. By inferring a global molecular interaction network containing information from all the different in vitro treatments, we have come up with a set of testable hypotheses about which factors could be important in the myogenic differentiation process.

Inflammatory myopathies- #3274

P15- 237- STATIN-INDUCED NECROTIZING AUTOINMUNE MYOPATHY . RECURRENCE WITH FIBRATE USE

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We report a 65 year old woman with medical history of Dysilpemia , no familly hystory of neuromuscular disease and no

consanguinity . She was treated during one year withatorvastatine 40 mg/day and presented sub-acute onset ( 1 month ) of

myalgia ,fatigability and lower muscle weakness , with inability for runn diftuse to run and climb stairs. Physical examination

demonstrated a Gowers sign and proximal lower limb weakness ( M3+ MRC scale ) and proximal upper limb weakness ( M4

MRC ). Electromyography revealed myopathic changes in the lower and upper limbs (small polyphasic and short duration motor

units ) and resting spontaneous activity ( fibrillations ) . The serum creatine kinase (CK) was very elevated ( 10284 IU/L) and the

only anormal findings in the routine laboratory assessment . Neoplastic and autoimmunity serologic screening including viral

hepatitis B and C and VIH were are normal or negative. She had a left deltoid muscle biopsy was consistent with a necrotizing

myopathy with isolated atrophic fibers and several necrotic fibers without inflammatory infiltrates and immunohistochemistry

ruled out muscular dystrophy . Oral prednisone was initiated and titrated up to a daily dose of 80 mg in June 2012 . It resulted in

a significant reduction of myalgia and weakness . In December 2012 the physical examination revealed normal muscle strength

( M5 MRC ) and serum CK levels were normal ( 116 U/I/L) . During 2013 the corticotherapy was threereduced and additional

metrotrexate was initiated with persistence of clinical improvement . In May 2013 the patient stopped the treatment . In

November 2013 she remains asintomatic with normal serum CK . In March 2014 treatment for dysilpemia was started with oral

gemfibrozil ( 600 mg ) . After 2 months she presented recurrence of myopathic sympotms and objetive clinical worsening ( myalgia

and fatigability ) and a significant increase of CK level ( 6500 UI/L) Oral gembrizolil was withdrawn and oral prednisone was

reestablished with a rapid disappearance of symptots and normalization of CK after 1 month of treatment ( 168 UI/L) . Two

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months later corticotherapy were tapered and additional therapy with Azathioprine (100 mg) was initiated with favorable clinic course with no adverse side effects after one year.

In summary we report a case of statin induced autoimmune necrotizing myopathy with a good outcome after treatment suspension and recurrence with gemfibrozil use.

**MYOPATHY STATIN FIBRATE**

**P16- Limb girdle muscular dystrophies / OPMD- N° 238 to N° 255**

Limb girdle muscular dystrophies - #2434

**P16- 238- A novel mutation in SGCA gene: clinical and genetic analysis of an Iranian family with LGMD2D**

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Sarcoglycanopathies constitute a subgroup of autosomal recessive limb girdle muscular dystrophies (LGMDs) which are caused by mutations in sarcoglycan (SGs) genes. SG proteins form a core complex consists of ?, ?, ? and ? sarcoglycans which are encoded by SGCA, SGCB, SGGG and SGCD genes respectively. Alpha-SGPs are the most frequent form of SGPs. Muscle biopsy studies in patients with sarcoglycanopathies have indicated that loss of one SG subunit leads to instability of whole SG complex.

Autozygosity mapping is a gene mapping approach which can be applied in large consanguineous families for tracking the defective gene in most autosomal recessive disorders.

In the present study, proband was a 9 year old girl from consanguineous parents. She was diagnosed at the age of 5 when she had problems climbing stairs. Her creatine kinase level was 16428 U/L. Proximal weakness and ankle contracture were also observed in the patient. Autozygosity mapping, using short tandem repeat (STR) markers linked to the SG genes, showed co-segregation of the phenotype with STR markers linked to the SGCA gene. Her muscle biopsy also suggested alpha sarcoglycanopathy. Mutation analyses revealed a novel homozygous deletion of 11 base pairs in exon 4 of this gene. This deletion causes a frameshift mutation followed by a stop codon at the fourth position after the changed codon. This will eliminate the expression of the downstream part of the extracellular domain of the protein. This domain has a critical role by associating with other molecules of dystrophin-glycoprotein complexes.

IHC studies combined with autozygosity mapping and mutation screening is an efficient diagnostic method in the sarcoglycanopathies.

**Alpha-sarcoglycan; Sarcoglycanopathy; Limb girdle muscular dystrophy; Autozygosity mapping; Immunohistochemistry**

Limb girdle muscular dystrophies - #2449

**P16- 239- Muscular dystrophies in Burkina Faso: a report of one case of dysferlinopathy**

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**Introduction**

Dysferlinopathies encompass a large variety of neuromuscular diseases characterized by the absence of dysferlin in skeletal muscle and an autosomal recessive mode of inheritance. So far, three main phenotypes have been reported: Miyoshi myopathy (MM), limb girdle muscular dystrophy type 2B (LGMD 2B), and distal myopathy with anterior tibial onset (DMAT). Although rare, dysferlinopathies occur frequently in the Middle East and the Indian subcontinent. Limb girdle muscular dystrophy is rare in Africa, specially in Burkina Faso. The objectives of this study is to report a case of dysferlinopathy occur in Burkina Faso.

**Clinical observation**

It is a case of a burkinabe patient, a teacher, born on 1984 who has consulted on March 2009 in neurology. He was suffering from walk troubles with falls, difficulties to be up, and muscular cramps with a progressive evolution since one year. In the past medical history, three cases of walk troubles have been registered. The neurological examination noticed a tetraparesy with a proximal predominance. The achilleen and osteo-tentinous kneejerk were abolished, so are the idiomuscular reflexes. Serum