"New targets to control skeletal muscle inflammation: MicroRNAs regulated by adiponectin"

Boursereau, Raphaël ; Abou Samra, Michel ; Lecompte, Sophie ; Deprez, Claire ; Noel, Laurence ; Brichard, Sonia

ABSTRACT

Although adipocytes are the main source of circulating adiponectin (ApN), several studies have now shown that ApN may be produced by the skeletal muscle in response to cellular stress. This induction could be a protective mechanism that counteracts inflammation, oxidative stress and cellular damage occurring during skeletal muscle injury. MicroRNAs (miRNAs) are small non-coding RNAs that control gene expression by inducing target mRNA degradation or blocking translation. In this work, we characterized miRNAs that may contribute to the anti-inflammatory action of ApN on skeletal muscle. To this end, we used ApN-knockout (KO) mice: one tibialis anterior muscle was electroporated with a plasmid coding for the ApN gene while the contralateral leg received a control plasmid. Mice were next challenged by lipopolysaccharide (LPS) to induce inflammation. Muscle electrotransfer of ApN gene induced anti-inflammatory effects: expression of markers of inflammation (TNFα, IL-1β) and oxidative s...

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Miller Fisher syndrome (MFS) is an acute polyradiculoneuritis regarded as an uncommon variant of Guillain–Barré syndrome (GBS). MFS is characterised by the acute onset of a clinical triad of ophthalmoplegia, cerebellar ataxia and areflexia. Atypical forms of MFS presenting as ophthalmoplegia without ataxia, with or without decreased deep tendon reflexes have been described in the literature in recent years. Case 1: A 6-year-old boy presented with acute onset of diplopia, ten days after he experienced diarrhoea and fever for one week. Neurological examination showed bilateral isolated sixth nerve palsy. Investigations including brain imaging, lumbar puncture were normal. Campylobacter jejuni serology showed elevated IgG and IgA. Analysis of anti-ganglioside antibodies by ELISA in serum obtained immediately after admission revealed high levels of anti-GQ1b, anti-GT1a and anti-GD3 IgG and IgM. We observed complete spontaneous resolution 7 weeks after onset. Case 2: A 4-year-old boy admitted with limited abduction of both eyes, as well as adduction paresis of the right eye. Two weeks before, the boy suffered from a febrile episode with diarrhoea during approximately one week. All investigations carried out on admission were normal. ELISA for anti-ganglioside antibodies was obtained 2 weeks after onset and revealed elevated titers of anti-GQ1b and anti-GT1a IgG and IgM. Serology was positive to C. jejuni. 2 months after onset, ophthalmoplegia had completely disappeared without any treatment. We report 2 cases of atypical MFS in children presenting as isolated ophthalmoplegia a few weeks following gastrointestinal infection. Identification of high titers of anti-GQ1b IgG associated with positive serology for C. jejuni enabled the diagnosis of atypical MFS. This paper highlights the relevance of measuring serum anti-GQ1b IgG level in the diagnostic work-up of acute isolated ophthalmoplegia of unknown aetiology in a child.

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G.P.413 Enhancement of myosin heavy chain class I (MHC I) mRNA expression in C2C12 myocyte by multivalent cations
Y. Mori*, 1, J. Yamaji1, 2, R. Hiroshima 1, T. Nakano 1, M. Watanabe 1, A. Miyazaki 1
1 Department of Rehabilitation, Kansai University of Welfare Sciences, Kashiwara, Japan; 2 Department of Nutrition Sciences, Kansai University of Welfare Sciences, Kashiwara, Japan; 3 Department of Clinical Pathology, Osaka Medical College, Takatsuki, Japan

Our previous study using differentiated C2C12 cells indicated that myosin heavy chain (MHC), interleukin-6 (IL-6) and heat shock protein 70 (HSP70) mRNA expression levels were significantly increased by the application of La3+ to the culture medium. The effects of La3+ on these mRNA levels might be considered as a result of calcineurin activation, because it was known that La3+ stimulates the activity of calcineurin. In the present study, we examined the effects of multivalent cations including La3+, Gd3+, or Ni2+ on expression levels of MHC I, IL-6, and HSP70 mRNA in C2C12 cells. C2C12 cells were induced to differentiate from myotubes by medium exchange to D-MEM containing 2% FCS. The cells were incubated in D-MEM containing 2% FCS with multivalent cations at the beginning of differentiation and removed after 24 hr, and were maintained in differentiation medium for 3 days. Our results are as follows: (1) The MHC I, IL-6, and HSP70 mRNA expression levels were significantly increased by La3+, but were decreased by cyclosporine A with or without La3+. (2) The MHC I mRNA expression level was significantly increased by the application of Gd3+ or Ni2+, although the HSP70 mRNA expression was not affected. (3) The IL-6 mRNA expression level was significantly decreased by the application of Ni2+, but was not affected by the application of Gd3+. These results indicated that La3+ in the culture medium flowed into the cytosol through some kind of ion channels, then upregulates these mRNA levels in calcineurin-dependent manner. The modulating mechanisms of the mRNA levels by Gd3+ or Ni2+ were still unclear. Further experiments need to be done to clarify the effects of multivalent cations on these mRNA expressions in C2C12 cells.

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G.P.414 Contribution of IL-6-dependent signalling mechanism to upregulation of MyHC IIB mRNA but not of MyHC IIA mRNA in mouse myocytes
J. Yamaji*, 1, Y. Mori 1, R. Hiroshima 1, M. Watanabe 1, A. Miyazaki 1
1 Department of Nutrition Science, Kansai University of Welfare Sciences, Kashiwara, Japan; 2 Department of Rehabilitation, Kansai University of Welfare Sciences, Kashiwara, Japan; 3 Department of Clinical Pathology, Osaka Medical College, Takatsuki, Japan

Previously, we reported the IL-6- and/or calcineurin-dependent augmentation of myosin heavy chain class I (MyHC I) mRNA expression and skeletal muscle modulators including IL-6 and HSP70. In the present study, we examined the effects of LaCl3, and chlorogenic acid as calcineurin activator on mRNA expression of MyHC II isoform, MyHC IIA and IIB, in C2C12 cells. Then our study yielded the following results: (1) The mRNA expression of MyHC IIB was significantly upregulated by IL-6 and by calcineurin-activator, chlorogenic acid and La3+, the same as that of MyHC I. (2) The MyHC IIA mRNA expression was increased by chlorogenic acid or La3+, but not by IL-6. (3) These mRNA expressions were decreased by calcineurin inhibitor, cyclosporine A, with or without chlorogenic acid. These results suggested that calcineurin signalling enhances both MyHC IIA and MyHC IIB mRNA, but that IL-6-dependent signalling mechanism contributes to upregulation of MyHC IIB mRNA but not of MyHC IIA mRNA in C2C12 cells.

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G.P.415 New targets to control skeletal muscle inflammation: MicroRNAs regulated by adiponectin
R. Boursereau *, M. Abou-Samra, S. Lecompte, C. Deprez, L. Noël, S. Brichard
EDIN, Université Catholique de Louvain, Bruxelles, Belgium

Although adipocyes are the main source of circulating adiponectin (ApN), several studies have now shown that ApN may be produced by the skeletal muscle in response to cellular stress. This induction could be a protective mechanism that counteracts inflammation, oxidative stress and cellular damage occurring during skeletal muscle injury. MicroRNAs (miRNAs) are small non-coding RNAs that control gene expression by inducing target mRNA degradation or blocking translation. In this work, we characterized miRNAs that may contribute to the anti-inflammatory action of ApN on skeletal muscle. To this end, we used ApN-knockout (KO) mice: one tibialis anterior muscle was electroporated with a plasmid coding for the ApN gene while the contralateral leg received a control plasmid. Mice were next challenged by lipopolysaccharide (LPS) to induce inflammation. Muscle electrottransfer of ApN gene induced anti-inflammatory effects: expression of markers of inflammation (TNFα, IL-1β) and oxidative stress (peroxyrionidine-3; PRDX3) were downregulated (~50%) in the muscle electroporated with ApN compared to the contralateral one. miRNA expression profiling revealed that ApN increased the expression of miR-711 (~150%), data which were validated by RT-qPCR. In murine myotubes (C2C12), ApN treatment also upregulated miR-711 and reduced gene expression of TNFα, IL-1β caused by LPS. Transfection of miR-711 mimic reproduced the anti-inflammatory effects of ApN, while using miR-711 inhibitor attenuated these effects. We found that miR-711 repressed 4 genes ( fadeIn, pi3kδ, tab1 and tollip) belonging to the toll-like receptor 4 signalling pathway, which is activated by LPS. In primary cultures of human myotubes, ApN treatment also stimulated the expression of miR-711. The anti-inflammatory effects of ApN appear to be
mediated at least in part by miR-711. These data may open new therapeutic perspectives to control muscle inflammation.

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G.P.416
Perifascicular pathology in eosinophilic fasciitis with muscle involvement

D. Pehl 1, C. Preusse 1, J. Rinneenthal 1, U. Schneider 2, A. Foucher 2, J. Aouizerate 2

1 Department of Neuropathology, Charité Universitätsmedizin Berlin, Berlin, Germany; 2 Department of Rheumatology, Charité Universitätsmedizin Berlin, Berlin, Germany

In 1974 Shulman described a disease characterized by fibrosis and inflammation of the muscle fascia and scleroderma-like skin changes, associated with hypergammaglobulinemia and blood eosinophilia. Eosinophilic fasciitis (EF) or Shulman syndrome is a rare disease of so far largely unknown etiology and pathophysiology. We could show a strong immunoreactivity for the mannose receptor CD206 expressed by macrophages dominating the inflammatory infiltrate in the peri- and epimysium of EF patients. Conversely, a predominant Th1 phenotype of the immune response with strong IFN-γ expression in the muscle and fascia tissue was observed at molecular level. Furthermore, the majority of EF patients exhibited a perifascicular pathology with upregulation of MHC class II in addition to upregulation of MHC class I, accompanied by a moderate perifascicular atrophy in a number of cases. Matching the rather low numbers of eosinophils seen in the tissue, there was no upregulation of IL-3, IL-5, IL-8, CCL5, CCL11, CCL24, and CCL26, cytokines and chemokines involved in activation and chemotraction of eosinophils. Capillary loss and hypoxia are assumed to be essential pathomechanisms leading to perifascicular pathology in dermatomyositis (DM), but we could not demonstrate signs of hypoxia in EF by immunohistochemical staining for HIF1α, or show a reduction in capillary density. There was also no upregulation of type I interferon-associated genes (such as ISG15) in EF patients, which are associated with perifascicular atrophy in adult DM. Therefore, we suggest a specific IFN-γ-driven mechanism of perifascicular pathology in Shulman syndrome, associated with MHC class II expression, distinct from the mechanisms involved in other forms of myositis with perifascicular pathology.

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G.P.417
Neuropsychological correlates of brain perfusion SPECT abnormalities in patients with macrophagic myositis

A. Van der Gucht 1, M. Aou Sefati 1, E. Itti 1, J. Aouizerate 2, A. Bachoud 2, F. Authier 1, 2

1 Henri Mondor Hospital, Creteil, France; 2 Team 10, Paris Est Creteil-University, Creteil, France

Patients with aluminum hydroxide adjuvant-induced macrophagic myositis (MMF) complain of arthromyalgias, chronic fatigue and cognitive deficits. This study aimed to characterize brain perfusion abnormalities in these patients. Brain perfusion SPECT was performed in 76 consecutive patients (aged 49 ± 10 y) followed in the Garches–Necker–Mondor–Hendaye reference center for rare neuromuscular diseases. Images were acquired 30 min after intravenous injection of 925 MBq 99mTc-ethylcysteinate dimer (ECD) at rest. All patients also underwent a comprehensive battery of neuropsychological tests, within 1.3 ± 5.5 mo from SPECT. Statistical parametric maps (SPM12) were obtained for each test using a correlation design between performance scores and brain perfusion, with adjustment for age, sex, handedness and socio-cultural level. Multivariate regression analyses revealed positive correlation between neuropsychological scores (mostly exploring executive functions) and brain perfusion in the posterior associative cortex, including cuneus/precuneus/occipital lingual areas, the periventricular white matter/corpus callosum, and the cerebellum, while negative correlation was found with amygdalo-hippocampal/entorhinal complexes. A positive correlation was also observed between brain perfusion and the posterior associative cortex when the time elapsed since last vaccine injection was investigated. Brain perfusion SPECT showed a pattern of cortical and subcortical abnormalities in accordance with the MMF-associated cognitive disorder previously described. These results provide a neurobiological substrate for brain dysfunction in aluminum hydroxide adjuvant-induced MMF patients.

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G.P.418
Wrist-worn accelerometer as innovative tool for longitudinal follow-up of idiopathic inflammatory myopathy patients: A pilot study

Y. Allenbach 1, F. Authier 2, N. Champtaux 1, L. Gilardin 1, B. Hervier 1, O. Benveniste 1, J.Y. Hogrel 1

1 Assistance Publique Hopitaux de Paris, Hôpital Pitié Salpêtrière, Internal Medicine, Sorbonne Universités, Université Pierre et Marie Curie, Paris, France; 2 Institut de Myologie, Université Pierre et Marie Curie, Paris, France

Idiopathic inflammatory myopathies (IIM) are disabling diseases. Disabilities may be due to muscular manifestations and/or to extra-muscular manifestations. Clinical tools for strength evaluation lack of reproducibility, and global extra-muscular assessment implies complex scores. In addition their ability to reflect the impact of the disease in the daily life remains elusive. An objective, simple and reliable tool is needed, especially regarding future clinical trials. Accelerometry provides the opportunity to objectively monitor motor activity over days during daily-life of patients. We aimed at testing accelerometer measurements to assess the changes in global physical activity of patients after treatment initiation. We have initiated a pilot study including five patients recently diagnosed for IIM. A wrist-worn accelerometer recording 15 days per month (study duration 6 months) was used after the initiation of treatment. The global movement quantity was obtained by computing the norm of the acceleration vector over recording days. Mean age of the patients was 47.7 years (Dermatomyositis = 1; Necrotizing myopathy = 3; Anti-synthetasis syndrome = 1). The mean manual muscle testing score (8 muscle groups: MMT8) was significantly lower by 75% in IIM patients compared to age and sex matched control groups. After one month of treatment, the global movement quantity increased by 15.6% on average, whereas MMT8 score increased by 6.4% and CK level decreased by 76.4%. These preliminary results showed that severe impairment of activity occurs in IIM patients, revealing more disabilities than MMT8 could suggest. Early important improvement of activity is detected after only one month of treatment whereas MMT changes are low. Together these results suggest that wrist-worn accelerometer is a promising objective and robust tool for home-monitoring of physical activity in patients with myositis.

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ADVANCES IN TREATMENT OF NEUROMUSCULAR DISEASE

I.I.9
Molecular regulation of muscle stem cell asymmetric division

M. Rudnicki

Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, Canada

Satellite cells located beneath the basal lamina of myofibers are required for the growth and regeneration of skeletal muscle. Molecular genetic studies in mice have established that a small subset of the satellite cell population comprises stem cells that are capable of reconstituting the satellite cell population following