BCMO1 as a potential target to improve skeletal muscle growth and repair

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Unravelling the cellular and molecular mechanism of GC-induced muscle atrophy will open new avenues to select GC with increased tissue selectivity, and identify new drug targets to combat muscle wasting.

Mot(s) Clé : Glucocorticoids, Atrophy, Mice model

N° 5#FR16 - BCMO1 as a potential target to improve skeletal muscle growth and repair

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The enzyme beta,beta-carotene-15,15' mono-oxygenase (BCMO1) cleaves provitamin A carotenoids into active vitamin A principally in liver and intestine. The BCMO1 gene is expressed at low level in the muscle tissue, including in myoblasts, but little is known about its function. In the chicken muscle, we observed that various bcmo1 expression levels are associated with different carotenoids contents. To investigate the potential role of BCMO1 on skeletal muscle, we assessed the impact of beta-carotene (BC), the prototype substrate of the BCMO1 enzyme, supplementation in vitro on proliferative primary avian myoblasts. Proliferation was evaluated by BrdU incorporation and by flow cytometry. The BrdU incorporation index was reduced and the proportion of G0/G1 cells increased following BC supplementation. Cell differentiation was evaluated by immunolabelling of sarcomeric myosin heavy chain (MHC). The proportion of sarcomeric MHC expressing cells and the differentiation index increased following BC supplementation despite the proliferative environment. The effects of BC were inhibited in the presence of DEAB, an inhibitor of retinaldehyde dehydrogenase. These results are in accordance with the hypothesis that the BCMO1 enzyme is active in myoblasts and can contribute to the retinoic acid production from BC. These data suggest that provitamin A could be used as a potential nutritional tool in dystrophic pathology to favor muscle repair or to improve the implantation of myoblasts in cell transplantation model.

Mot(s) Clé : BCMO1 enzyme, myogenesis

N° 6#GB12 - Impaired mitochondrial function and reduced energy cost as a result of severe muscle damage

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Neuromuscular electrostimulation (NMES) exercise induces severe muscle damage but the corresponding effects on muscle energetics remains to be determined. The aim of the study was to determine whether NMES exercise alters muscle energetics at rest and during a submaximal voluntary exercise. 31P magnetic resonance spectroscopy measurements were performed in thirteen healthy males during a standardized rest-exercise-recovery protocol before (D0), two days (D2) and four days (D4) after NMES exercise on knee extensors. Changes in kinetics of phosphorylated metabolite concentrations (i.e., phosphocreatine [PCr], inorganic phosphate [Pi] and adenosine triphosphate [ATP]) and pH were assessed to investigate aerobic and anaerobic rates of ATP production and energy cost of contraction (Ec). A significant decrease in resting pH was determined (-0.04 pH.unit and -0.03 pH.unit, at D2 and D4 respectively). [PCr] recovery rate decreased at D2 (-21%) and D4 (-23%) in conjunction with a diminished total rate of ATP production at D4 (-18%) mainly due to an altered aerobic ATP production. Paradoxically, Ec was decreased at D4 (-21%). Overall, severe muscle damage led to intramuscular acidosis in resting muscle and mitochondrial impairment in exercising muscle. Alterations of non-contractile processes and/or adaptive mechanisms might account for the decreased Ec.

Mot(s) Clé : Magnetic resonance spectroscopy (MRS), ATP production

We demonstrated in vitro a functional interplay between ECs and MPCs as: i) both cell type attract each other in migration assay, suggesting the secretion of specific attractive factors; ii) ECs strongly stimulate MPC differentiation, iii) MPCs promote angiogenesis, i.e. differentiation of ECs vessel-like structures. These results were confirmed in vivo, in which MPCs specifically promote the formation of functional vessels in a dose-dependent way. These results show that myogenesis and angiogenesis take place together. Several molecular candidates regulating angiogenesis/myogenesis coupling, including transcriptomic analysis of ECs and MPCs sorted at different time points during muscle regeneration, are under investigation in functional assays.

Collectively our results show that specific interactions between MPCs and ECs couple myogenesis and angiogenesis during muscle regeneration. These interactions may be altered in degenerative myopathies, where we already demonstrated strong perturbations of the vascular network associated with functional alteration (weaker muscle perfusion).

Mot(s) Clé : Myogenic precursor cells, Endothelial cells

Session 2 - Jeudi 20 Novembre 17h45/19h30

N° 1#GB13 - HACD1, a regulator of membrane composition and fluidity, promotes myoblast fusion and is essential for skeletal muscle growth

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The reduced diameter of skeletal myofibers is a hallmark of several congenital myopathies. However, the mechanisms underlying this defect remain elusive. In this study we investigate the role of HACD1, involved in elongation of long chain fatty acids, in muscle fiber formation. In humans and dogs, HACD1/PTPLA deficiency leads to a congenital myopathy with fiber-size disproportion and a generalized muscle weakness. Through analysis of HACD1-deficient dogs, mice, and C2C12 models, we provide evidence that HACD1 promotes myoblast fusion during muscle development and regeneration. We further demonstrate that differentiating myoblasts dynamically express a muscle-specific, Hacd1 full-length splice isoform encoding the only catalytically active protein, essential for myoblast fusion. Upon HACD1 induction, membranes of differentiating myoblasts were less rigid, contained increased concentrations of ≥C18 and monounsaturated fatty acids and decreased concentration of lysophosphatidylcholine, a potent inhibitor of myoblast fusion. Notably, adding of candidate fatty acids to HACD1-deficient myoblasts promoted their fusion. Our results suggest that muscle-specific splicing of Hacd1 increases myoblast membrane permissiveness to fusion via the dynamic modification of its lipid composition, thereby prompting muscle fiber growth. This work also highlights the possibility that defective myoblast fusion may play an important role in other congenital myopathies.

Mot(s) Clé : Congenital myopathies, Muscle development

N° 2#FR35 - Muscle niche ensures survival and reactivation of dormant Adult Muscle Precursor cells in Drosophila

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How stem cells specified during development keep their non-differentiated quiescent state, and how they are reactivated, remain poorly understood. Here we applied a Drosophila model to follow in vivo behavior of Adult Muscle Precursors (AMPs), which share several features with vertebrate muscle stem cells. We report that emerging AMPs display homing behavior, and that muscles act as their niche by protecting dormant AMPs from apoptosis. We observed that the AMPs contact muscle fibers by sending out thin

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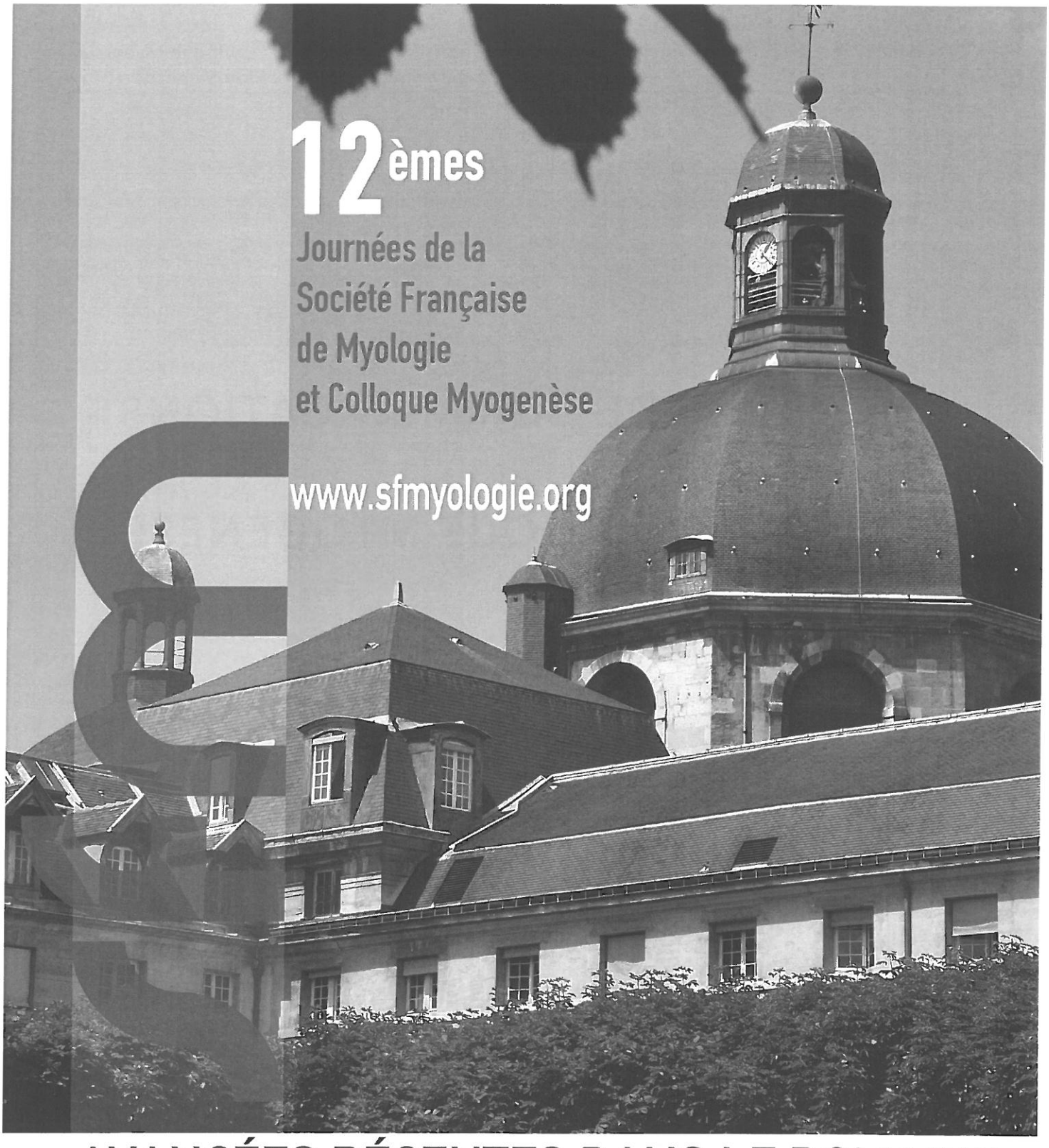

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PARIS - GHU PITIÉ-SALPÊTRIÈRE - 20/21 NOVEMBRE

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