cosmids in sets of three, we were able to conclude that unc-100 lies on one of these three cosmids: ZK524, T28F4 and C26C6. We are currently performing single cosmid rescue experiments to determine which of the three unc-100 lies on. To further accelerate identification of the unc-100 gene sequence, we are conducting whole genome deep sequencing of unc-100 (su149).

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Alterations on Striated Muscle Caused by Anabolic Androgenic Steroids Associated with a Selective β-adrenoceptor Blocker.

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The effects of the association of nandrolone with metoprolol on striated muscle were investigated. Forty male Wistar rats were randomly distributed into four groups: control, treated with nandrolone 10mg/kg Biweekly, treated with metoprolol 1mg/kg/day, and treated with both nandrolone and metoprolol for seven weeks. Left ventricle, soleus, and gastrocnemius sections were cut on a cryostat (5µm), and stained with hematoxylin and eosin, or picrosirius red. Digital images were captured and analyzed by software. Cross-sectional area, diameter, number of myonuclei per fiber, central myonuclei, splitting cells, myonuclear domain, percentage of conjunctive tissue, and serum testosterone were measured. Glucocorticoid (GR) and androgen receptor (AR) were analyzed by immunodetection. An increase was seen in the morphometric parameters analyzed in both cardiac and striated fibers from animal treated with nandrolone. Metoprolol partially restored the cardiac hypertrophy caused by nandrolone without reducing the final percentage of conjunctive tissue. However, the anabolic effect of nandrolone was not reverted by metoprolol on the striated fiber. Nandrolone administration increased serum testosterone levels and up-regulated the expression of AR whereas down-regulated GR expression ($P<0.05$). We conclude that; (1) the hypertrophic effects caused by nandrolone treatment are accompanied by a higher proportion of conjunctive tissue in cardiac and skeletal muscles, (2) metoprolol administration has a positive effect on the cardiac concentric hypertrophy caused by the steroid hormone, and (3) likely competitive mechanisms of metoprolol in addition to up-regulation of beta-adrenoceptors could have been responsible for the increased fiber size on skeletal muscle after beta1-blocker treatment.

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Can the Prostaglandin 15Δ-PGJ2 Influence Skeletal Muscle Regeneration?

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Many actors classically known to be involved in the inflammatory response can also play an important role in tissue regeneration. Cyclooxygenase-2 (COX-2) is a striking example since there are growing evidences that COX-2-derived prostaglandins could have anti-inflammatory effects. In fact, 15Δ-PGJ2, a PGH2-derived metabolite, has been postulated to be a key actor in the resolution of inflammation and can stimulate fibroblast proliferation. OBJECTIVE: to evaluate if 15Δ-PGJ2 can stimulate L6 myoblast proliferation In Vitro and accelerate skeletal muscle regeneration In Vivo and investigate the mechanism underlying these effects. METHODS: In vitro: L6 myoblasts were submitted to proliferation assays with 15Δ-PGJ2, DP1 agonist and DP1 and DP2 antagonists. In vivo: Female rats were injured with bupivacain in the tibialis anterior muscle, treated with 15Δ-PGJ2 and sacrificed at days 5, 10 and 15. The cross sectional area (CSA) of myofibers and the number of centrally nucleated fibers (CNF) were obtained from muscle sections stained with hematoxyline/eosine while the density of macrophages ED1+ and ED2+ was obtained by immunochemistry. Protein content of myoD and myogenin was evaluated by western blotting. RESULTS: In Vitro cell proliferation was significantly increased in a dose-dependent manner by 15Δ-PGJ2. DP1 and DP2 antagonists inhibited the 15Δ-PGJ2-induced stimulation of myoblast proliferation by 84 ± 17 % and 111 ± 20%, respectively. Surprisingly, DP1

agonist failed to stimulate myoblast proliferation. In Vivo treatment with 15Δ-PGJ2 tended to increase the CSA of injured fibers at day 5 when compared to placebo (776 ± 102 μm2 vs 863 ± 67 μm2), but this effect was lost at day 10 and 15. CNF tented to increase with treatment at day 5, 10 and 15. Preliminaries results showed that 15Δ-PGJ2 modulated the expression of myoD and myogenin. In summary, 15Δ-PGJ2 can accelerate proliferation of L6 myoblast In Vitro and this effect could be through stimulation of DP1 and DP2 receptors. The tendency to increase CSA and the number of CNF following treatment with 15Δ-PGJ2 suggests that this prostaglandin could shorten inflammation and/or stimulate regeneration. Supported by grants from NSERC and CIHR.

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Incomplete Functional Redundancy of Obscurin and Obscurin-like 1 (OBSL1) in Striated Muscle Development.

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Background: Obscurin and OBSL1 are orthologues of the invertebrate Unc-89 gene. In C. elegans, mutation or loss of Unc-89, a giant cytoskeletal protein with both structural and signaling properties, is associated with severe impairment of locomotion and the absence of organized M bands in striated muscle (Waterston et al., 1980). Yet, mice lacking obscurin (Lange et al., 2009) and humans lacking OBSL1 (Hanson et al., 2009) do not demonstrate significant cardiac or skeletal myopathy, suggesting a functional redundancy of the two related proteins. Objectives: In this study, we examined the unique and shared contributions of obscurin and OBSL1 to striated muscle development and myofibril assembly using In Vivo and In Vitro models. Methods: We used morpholino antisense oligonucleotides to reduce expression of obscurin and OBSL1, individually and in combination, in developing zebrafish embryos. Comparison to mammalian models was performed in differentiating C2C12 myoblasts and remodeling adult rat cardiac myocytes. Results: Zebrafish embryos depleted of obscurin a commonly displayed abnormalities of somite segmentation and myofibril alignment that were not noted in embryos lacking OBSL1. Embryos that lacked OBSL1 shared some features with the human OBSL1 deficiency syndrome in that the embryos were shorter with craniofacial abnormalities that were not noted in response to obscurin depletion. Effects of OBSL1 reduction on cardiac structure and function were strain-dependent with cardiac hypoplasia and pericardial edema in those more severely affected. In Vitro models demonstrated that, although obscurin and OBSL1 localized to the M bands of myofibrils, their spatio-temporal distribution suggested both shared and unique functions. Conclusions: Obscurin and OBSL1 have both shared and unique roles in striated muscle development and myofibril assembly. Their ability to compensate for each other appears to be context- and species-dependant. Since OBSL1 lacks the signaling properties of obscurin, it is likely that other cytoskeletal and signaling proteins, outside the obscurin gene family, provide a functional redundancy that may compensate for the loss of obscurin or OBSL1 in some settings.

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Myofibril Maturation Is Coordinated with Cardiomyocyte Elongation during Cardiac Chamber Formation.

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Embryonic hearts increase in size and contractile force to cope with rising demand during development. As the heart tube transforms into cardiac chambers, cardiomyocyte size expands to create chamber curvatures. To investigate whether myofibrils mature while cardiomyocytes expand, we used immunofluorescence to examine Z disc dimensions and cell contours in embryonic zebrafish hearts. In wild-type embryos, ventricular outer curvature cardiomyocytes gradually expand in size while simultaneously increasing their myofibril thickness. Thus, it seems that embryonic cardiomyocytes undergo hypertrophic growth similar to that observed in cardiomyocytes in culture, which increase their myofibril content in concert with their size