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Meeting synopsis: advances in skeletal muscle biology in health and disease (Gainesville, Florida, February 22nd to 24th 2012) – day 2: "muscle diseases and regeneration" and "clinical/translational research"

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Day 2 of the "Advances in Skeletal Muscle Biology in Health and Disease" conference consisted of 14 speakers across two sessions – "Muscle diseases and regeneration" and "Clinical/translational research." The synopsis below outlines some of the main findings and future directions presented in these two sessions.

MUSCLE DISEASES AND REGENERATION

A major priority area in skeletal muscle research is that of muscle regeneration following damage or degenerative disease, or in the context of primary muscle myopathies. This first session on Day 2 of the symposium therefore highlighted the latest findings and future directions by scientists at the cutting edge of the muscle degeneration/regeneration field including Drs. Denis Guttridge, Ashok Kumar, Da-Zhi Wang, Maury Swanson, Erika Geisbrecht, Sweta Girgenrath, and Paula Clemens. Dr. Guttridge presented new results specific to the alternative pathway of NF-kappaB. Earlier published data from the Guttridge laboratory using C2C12 cells showed that alternative NF-kappaB signaling is activated in late stage myogenesis and that this activation is associated with mitochondrial biogenesis. Dr. Guttridge presented new work, using both gain and loss of function components of the NF-kappaB alternative pathway, that regulation of mitochondrial biogenesis by alternative NF-kappaB occurs *in vivo*. In addition, he showed that this regulation occurred through the transcriptional control of PCG-1beta, itself a well established regulator of mitochondria. During myogenesis, the RelB subunit of the alternative pathway binds to two enhancer sites in the first intron of PCG-1beta and this binding activates transcription through chromatin modification in the proximal promoter region of PCG-1beta. Lastly, Dr. Guttridge revealed that activation of alternative signaling during myogenesis is under the control of mTOR and that mTOR regulation of PCG-1beta occurs through NF-kappaB.

Dr. Kumar described his findings showing that the expression and activity of various matrix metalloproteinases (MMPs) are dysregulated in skeletal muscle of dystrophin-deficient mdx mice. Treatment of mdx mice with Batimastat, a MMP inhibitory peptide, improved pathology and muscle contractile functions. Moreover, Dr. Kumar presented findings implicating MMP-9 as one of the most important MMPs involved in myofiber hypertrophy and necrosis, inflammation, and fibrosis in dystrophic muscle of mdx mice. Further, he also noted that increased levels of MMP-9 cause cardiomyopathy in 1-year-old mdx mice.

Dr. Geisbrecht presented work on the signaling and cell adhesive events that underlie defects in the formation and/or maintenance of the myotendinous junction (MTJ), which result in progressive myopathies in vertebrate models and humans. Dr. Giesbrecht's laboratory uses the fruit fly, *Drosophila melanogaster* as a model to identify and characterize new genes required for proper MTJ formation. Her group identified Moleskin (Msk) as the vertebrate ortholog of Importin-7. Loss of Msk function results in muscles that detach after muscle contraction begins. The canonical role of Importin-7/Msk is in nuclear import. However, in embryonic MTJ formation, Msk protein localizes to the sites of muscle-tendon attachment and is required for muscle to tendon signaling through the epidermal growth factor receptor signaling pathway to mediate stable formation of the MTJ. Future studies in the Geisbrecht laboratory will focus on Msk-interacting proteins to further define how proteins are shuttled and retained at the MTJ.

Dr. Girgenrath discussed her data on MDC1A, which is a severe form of congenital muscular dystrophy characterized by hypotonia, muscle weakness, and premature death. MDC1A results from deficiency in the laminin alpha 2 chain of laminin-211, an extracellular matrix protein mainly found in skeletal muscle and Schwann cells. Defects in laminin-211 cause major disruption of structural stability and signal transduction that leads to apoptosis, failed regeneration, and chronic inflammation. An emerging idea in the study of multiple diseases is that different pathological processes are intimately connected and can even amplify one another; this theory may apply to MDC1A. Dr. Girgenrath presented data showing that while targeting regeneration or apoptotic processes alone result in measurable improvement in the pathology of MDC1A/DyW mice, a combinatorial therapeutic approach that targets both results in marked improvement in pathology with larger, more uniform myofiber size as well as improved regeneration and reduced fibrosis. Dr. Girgenrath's results suggest that dual therapy has promising potential as an effective treatment for MDC1A.

Dr. Clemens showed her findings on NF-kappaB signaling in Duchenne muscular dystrophy (DMD). The chronic activation of NF-kappaB in dystrophic muscle leads to (1) infiltration of macrophages, (2) up-regulation of the ubiquitin-proteasome system, and (3) down-regulation of the helix-loop-helix muscle regulatory factor, MyoD. Dr. Clemens has characterized the role of A20 (TNFAIP3), a critical negative regulator of NF-kappaB, in muscle regeneration. A20 is highly expressed in regenerating muscle fibers and knock down of A20 impairs muscle differentiation *in vitro*, suggesting that A20 expression is critically important

for regeneration of dystrophic muscle tissue. Furthermore, down-regulation of the classical pathway of NF-kappaB activation is associated with up-regulation of the non-classical pathway in regenerating muscle fibers suggesting a mechanism by which A20 promotes muscle regeneration. Dr. Clemens' novel findings demonstrate the important role of A20 in muscle fiber repair and suggest the potential of A20 as a therapeutic target to ameliorate the pathology and clinical symptoms of DMD.

CLINICAL/TRANSLATIONAL RESEARCH

The final session covered bench to bedside translational research, presented by Drs. Marcas Bamman, Danny Martin, Bill Durham, Michael Toth, Hermien Kan, Glenn Walter, and Barry Byrne. Dr. Bamman discussed human muscle mass regulation with a focus on resistance training as the most readily available strategy to promote muscle regrowth following atrophy, but one that is not equally effective across individuals. He described the application of *K*-means cluster analysis to identify human responder phenotypes, which has led his laboratory to reveal a number of processes that appear to be integral to the myofiber hypertrophy adaptation in humans, including factors that promote protein synthesis and myonuclear addition. Dr. Bamman then described a reverse translational ("bedside to bench") approach that his laboratory has utilized to test the impact of observations from the human cluster model via targeted genetic manipulation experiments of translational signaling proteins *in vitro* and *in vivo* (in mice). Lastly, Dr. Bamman described the power of this *K*-means clustering approach for discovery, presenting as yet unpublished findings from genomic microarrays and proteomic studies using 2D-DIGE.

Dr. Martin presented work on the effect of intraoperative hemidiaphragm stimulation on mitochondrial respiration in humans. Recent work in animals and humans has documented that the inactive diaphragm undergoes rapid dysfunction including loss of contractile force and mitochondrial function. Dr Martin's results show that electrically stimulating the human hemidiaphragm for 1 min every hour during cardiac surgery leads to improved state II and state IV mitochondrial respiration when compared to the unstimulated hemidiaphragm. The results of a recently published clinical trial by Dr. Martin and his group examining the effects of inspiratory muscle strength training were reviewed. In this trial, patients who had received mechanical ventilation for approximately six continuous weeks were weaned at a greater rate following a specific inspiratory muscle strength training program, compared to a usual care group.

Dr. Durham presented data collected in collaboration with Dr. Melinda Sheffield-Moore's group. They found that skeletal muscle utilization of infused amino acids for protein synthesis is less efficient in older versus younger men following endurance-type exercise. Despite reduced skeletal muscle microvascular perfusion, this anabolic resistance was not due to reduced availability of amino acids for skeletal muscle protein synthesis, as circulating, interstitial, and intracellular amino acid concentrations were equal or higher in older men than in younger men. Markers of metabolic and oxidative stress as well as sarcolemmal damage were greater in the older individuals, raising the possibility that hemodynamic effects on these variables may contribute to the observed age-related anabolic resistance.

Dr. Toth discussed his findings on myosin myopathy of acute and chronic disease. With the development of chronic disease in humans, there are quantitative and qualitative changes in skeletal muscle myosin. These myosin phenotypes are evident functionally at the molecular and cellular level and may contribute to reduced whole muscle function. In this context, alterations in myosin content and functionality may represent a molecular mechanism whereby acute and chronic diseases impair skeletal muscle function and increase the risk for the development of physical disability.

The meeting concluded with a presentation from Dr. Byrne on his gene therapy work in Pompe disease. Pompe disease is an inherited condition of acid alpha-glucosidase (GAA) deficiency resulting in lysosomal accumulation of glycogen in all tissues. This glycogen accumulation leads to muscle dysfunction and profound muscle weakness, ultimately leading to cardiorespiratory failure. Dr. Byrne presented very encouraging pre-clinical and clinical findings from his laboratory showing that introduction of the normal GAA gene into muscle cells via gene therapy produces GAA protein at levels sufficient to reduce glycogen accumulation and improve measures of respiratory function.

SUMMARY

This is a very exciting time for researchers of adult skeletal muscle as we learn more about the incredibly plastic nature of skeletal muscle and begin to understand the signaling pathways regulating that plasticity. Moreover, the translation of skeletal muscle bench work to bedside is now an ongoing reality rather than just a buzz phrase. Despite this, adult skeletal muscle adaptations in health and disease have traditionally received largely peripheral attention in the context of both research and patient care. Therefore one of the primary purposes of this meeting was to bring together leading researchers that share a passion for adult skeletal muscle plasticity, with the aim of stimulating innovative and new directions that will advance this important field. We hope the interactive and friendly environment facilitated the attainment of this goal. Thanks to the efforts of the participants and organizers alike, we are confident that new collaborations will stem from, and ongoing collaborations were solidified at, this meeting. Finally, we expect this meeting will take place again in 2014 and hope it will be as fruitful and well-received as it was this year.

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