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Regulation of skeletal muscle size, regeneration and repair

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This session was very interactive with much discussion among the speakers and participants at the Workshop. The speakers were charged with presenting their research programs in a way to highlight potential commonalities between bone and muscle research such as the catabolic cascade of the NF-kB pathway in osteoporosis and muscle atrophy/cachexia. In general, this was accomplished but the ensuing discussion did lead to recognition of gaps of knowledge in areas that would greatly facilitate bridging research programs. Specifically, the two areas that stood out as exciting opportunities for collaborative and integrative research included the role of Vitamin D in skeletal muscle health and understanding myopathies associated with osteoarthritis (OA) and rheumatoid arthritis (RA). In the end, there was much agreement that exciting collaborative research opportunities, with significant translational potential, exist between muscle and skeletal tissue biologists.

Johnny Huard spoke on "Regenerative medicine based on muscle stem cells". There was a significant amount of discussion and interaction during this talk regarding the role of muscle-derived stem cells (MDSCs) and therapeutic uses of decorin in muscle repair. In particular, the potential for the MDSCs for contribution to different skeletal lineages was pursued. An intriguing finding from Dr. Huard's study was the contribution of the host environment to the incorporation of the MDSCs to the endogenous muscle. Since the MDSCs do not incorporate into normal healthy muscle, it is important to identify factor(s) in the site of muscle injury that facilitate the stem cell function in repair. The association of the MDSCs with blood vessels suggested the potential for isolating these multipotent cells from other tissue systems in the body. Dr. Huard also presented data on the therapeutic use of decorin for aiding regeneration and repair of skeletal muscle.

Susan Kandarian's talk dealt with "Multiple triggers lead to concomitant loss of bone and muscle including reduced loading, aging, and systemic inflammatory conditions". Dr. Kandarian made a point of focusing on the common pathologies, loss of tissue, which both muscle and bone exhibit in disease and disuse. She brought forward her work on the transcription factor, nuclear factor of kappaB (NF-kB), as a possible common molecular mechanism linked to osteoporosis and skeletal muscle atrophy. There was discussion about the potential role of inflammation seen in (RA) and/or aging with induction of NF-kB in muscle and whether that could contribute to the myopathies associated with RA/aging. To date there are no studies that have looked for any common molecular triggers in RA and muscle disease. Dr. Kandarian noted that in the model of muscle atrophy that her lab employs, unloading, the induction of NF-kB is not associated with inflammation. This raised some interesting discussions about the immune vs. non-immune cell-dependent atrophy signaling that may be shared by muscle and bone. The potential for studying upstream regulators of NF-kB in both tissues in models of aging, disuse and arthritis could provide important and novel insight with clinical implications. Upstream regulators such as IkappaBalpha and Nedd4 were discussed. However, the NF-kB pathway is very complex with multiple upstream regulators and downstream effectors so the rest of the discussion highlighted the lack of understanding of this crucial pathway and the need for more research that might take advantage of the common responses of muscle and bone. Her work drew significant interactions with skeletal tissue scientists interested in the pathologies seen in aging and conditions such as rheumatoid arthritis.

"Regulation of muscle size in humans: Role of myostatin?" was Marcas Bamman's topic. Dr. Bamman presented an impressive range of studies on issues relating to regulation of skeletal muscle size in humans. His working model for these experiments includes important roles for the requirement of satellite cell proliferation and protein synthesis. Dr. Bamman provided some very interesting results

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from a large cohort of humans and resistance exercise showing differences among humans in their response to a training program. This is an issue that has been suggested, but to date has had very little evidence. His results from the responder-non-responder populations suggested that myostatin is not likely a good predictor of muscle mass in humans but that changes in a splice variant of IGF1 might be useful. Whether changes in bone with training can also be sorted into these two populations and whether these populations would be the same was an interesting point of speculation but no clear molecular target(s) have been identified.

Karyn Esser presented "Mechanical regulation of growth signaling in skeletal muscle: Role of mTOR". She presented data from her lab regarding the signaling mechanisms linking mechanical loading of muscle to protein synthesis and growth. A significant focus of her talk was on establishing the unique pathway by which passive mechanical strain activates signaling through mTOR. Whether this pathway exists in bone cells is not clear but is an interesting question for future research. It is clear that other cells, not normally known to exhibit anabolic responses to loading, do not show a link between mechanical strain and activation of mTOR. Clinical concerns related to this presentation were discussed and included the potential for Vitamin D to modulate mTOR signaling. Also, since models of muscle atrophy are associated with decreased mTOR signaling, additional discussion related to whether models of bone and joint disease might result in diminished mTOR signaling. Again, this is an area of great potential research between the fields. Finally, some discussion was had about the mTOR inhibitor, rapamycin, which is being used for the treatment of different cancers. While this treatment could be beneficial for slowing the growth of cancer, it could be deleterious for both muscle and skeletal tissue loss in those patient populations.