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**Title of Presentation: Potential roles for HIF-1α and TGF-β in the modulation of angiogenic factors in response to repetitive tensile loading**

**Abstract**

Tendon disorders are a significant cause of pain and morbidity amongst athletes, workers and the general public. Tendinopathy is often viewed as the result of failed or inadequate healing response through repetitive overuse. Previous authors have suggested there may be an association between pain and neurovascular changes resulting from tendon overuse in tendinopathy patients. In order to examine the effects of repetitive overuse on the expression of angiogenic genes which regulate neovascularization in tendinopathy, primary human tendon cells were subjected to cyclic strain.

By using a Flexcell® Tension System, isolated tendon cells from human hamstring tendons (excess ACL autograft material) were exposed to cyclic tension (1Hz frequency and 10% strain). MTS and tube formation assays were conducted with conditioned media in order to evaluate the proliferative and angiogenic activity of factors released by tenocytes. DMOG and A83-01were used to stabilize HIF-1α and inhibit TGF-β, respectively. RNA samples were isolated at different time points and gene expression was evaluated by conventional qPCR and qPCR array. Western blotting was also conducted to measure the relative amounts of target proteins.

Initial experiments showed that cyclic strain of two-dimensional primary tenocyte cell cultures increased the expression of VEGF, bFGF and Cox-2. But, by increasing the time course, VEGF, bFGF and Cox-2 were progressively downregulated. Angiogenic profiling of tendon cells by qPCR array identified a number of other genes (ANGPTL4, FGF-1, TGFα, VEGF-C and SPHK1) that appear to respond to tensile loading in a similar pattern. Upregulation of these factors may be responsible for an observed increase in proliferation and angiogenic activity of HUVEC cells. Our preliminary results show that ANGPTL4 expression was upregulated by HIF-1α and blocked by a TGF-β inhibitor.

It seems that the early response of tendon cells to overuse tensile loading leads to an upregulation of angiogenic factors which may play a role in tissue homeostasis following periods of overuse. HIF-1α and TGF-β pathways may be involved in this response and might modulate the expression of ANGPTL4. Future studies will unravel the mechanism and also the function of the ANGPTL4 protein in angiogenesis and matrix remodeling in tendons.