The involvement of the TNF-alpha system in skeletal muscle in response to marked overuse

Lina Renström

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i sal N320, Naturvetarhuset, fredagen den 8 december, kl. 09:00. Avhandlingen kommer att försvaras på svenska.

Painful conditions having the origin within the musculoskeletal system is a common cause for people to seek medical care. Between 20-40% of all visits to the primal care in Sweden are coupled to pain from the musculoskeletal system. Muscle pain and impaired muscle function can be caused by muscles being repetitively overused and/or via heavy load. Skeletal muscle is a dynamic tissue which can undergo changes in order to fulfill what is best for optimal function. However, if the load is too heavy, morphological changes including necrosis, as well as pain can occur. The extension of the skeletal muscle is the tendon. Tendinopathy refers to illness and pain of the tendon. The peritendinous tissue is of importance in the features related to tendon pain. Common tendons/origins being afflicted by tendinopathy/pain are the Achilles tendon and the extensor origin at the elbow region.

Tumor necrosis factor alpha (TNF-alpha) is a cytokine that is involved in several biological processes. It is well-known for its involvement in the immune system and is an important target for inflammatory disorders such as rheumatoid arthritis. It is not known to what extent the TNF-alpha system is involved in the process of muscle inflammation and damage due to overuse.

Studies were conducted on rabbit and human tissue, tissues that either had undergone an excessive loading activity or tissue that was removed with surgery due to painful conditions. The tissues were evaluated via staining for morphology, in situ hybridization and immunofluorescence. Unilateral experimental overuse of rabbit muscle (soleus muscle) led to morphological changes in the soleus muscle tissue bilaterally. The longer the experiment extended, the more was the tissue affected. This included infiltration of white blood cells in the tissue (myositis) and abnormal muscle fiber appearances. TNF-alpha mRNA was seen in white blood cells, in muscle fibers interpreted to be in a reparative stage and in white blood cells that had infiltrated into necrotic muscle fibers. There was an upregulation in expressions of TNF receptor type 1 (TNFR1) and TNF receptor type 2 (TNFR2) in muscles that were markedly overused, with expressions in white blood cells, fibroblasts, blood vessel walls and muscle fibers. Immunoreactions for the receptors were seen in nerve fascicles of markedly overused muscles but only occasionally in normal muscles. The upregulations were seen for both experimental and contralateral sides. Overall the two receptors showed somewhat different expression patterns. Tendinopathy is associated with an increase in blood flow and infiltration of white blood cells in the tissue adjacent to the tendon. It is called the peritendinous tissue and is also richly innervated. The white blood cells and the blood vessels walls in this tissue were showing immunoreaction for TNFR1 and TNFR2. Two types of nerve fascicles were found in this tissue, one normally appearing when staining for nerve markers and one type with signs of axonal loss. The latter had clearly strong immunoreactions for TNFR1 and TNFR2.

The findings suggest that the TNF-alpha system is involved in both myopathies occurring due to overuse and in features in the peritendinous tissue in the tendinopathy situation. TNF-alpha and its receptors seem to be involved in degeneration but also in regeneration and healing of the tissue. The findings also suggest that TNF-alpha has effects on nerves showing axonal loss. The changes in the TNF-alpha system were seen both on the experimental side and contralaterally.

Keywords
TNF-alpha, TNFR1, TNFR2, muscle damage, myositis, peritendinous tissue, tendinopathy