

## **AGING INDUCED CHANGES IN RAT MUSCLE TRANSCRIPTOME**

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Loss of muscle mass and strength with aging occurs in all animals studied to date and is a major health problem in humans. We have used an established rodent model of sarcopenia, the LOU/c/jall rat (extensive sarcopenia without obesity), to examine the role of chronic inflammation in the progression of sarcopenia. Gastrocnemus muscles have significant loss of mass with age after 24 months, and this tissue was examined at 7 months (young adult), 18 months (mature adult), and 27 to 30 months (old). Histology showed that there was a significant increase in macrophages and fibroblasts in old rats, an increase in fibrosis evidenced as %area connective tissue, and changes in fiber shape; all indicative of chronic inflammation. However, there was also fiber type grouping which is due to re-innervation. Ultrastructural analysis showed myofibril thinning which is common in polymyositis, thickened basal lamina, mitochondrial aggregation, and lipofuscin accumulation. To determine the regulation of sarcopenia, transcriptome analysis using Affymetrix arrays was performed on the three ages. There were approximately 31,000 genes on the array of which 16,000 were expressed in these muscle samples, and 1100 were differentially expressed in old animals. Some of the highlighted changes which compare and contrast this model to other transcriptome studies of muscle aging are few changes in extracellular matrix and the proteasome system. We did find extensive changes in expression of amyloid protein, cathepsin proteases, complement proteins, and the Fc receptor-immunoglobulin pathway. Classic sarcopenia markers including IGF-1, lamin A, beta-glucuronidase and metallothionein changed expression. In conclusion, these studies support that chronic inflammation and re-innervation are typical of aging muscle pathology in the Lou rat, and that these changes are at least partially due to genes regulating the cathepsin proteases, cytokines and complement mediated inflammation, and both the IGF and TGF hormone pathways.