7 MUSCLE WASTING IN HTNF^{TG} MICE, AN ANIMAL MODEL FOR RHEUMATOID ARTHRITIS, DUE TO INCREASED CATHEPSIN L EXPRESSION

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Objective To investigate skeletal myopathy in a chronic inflammatory, erosive animal model for rheumatoid arthritis, the human tumour necrosis factor transgenic (hTNF^{TG}) mice.

Methods To evaluate whether hTNF^{TG} mice are suffering from skeletal muscle atrophy, the authors isolated Triceps surae muscles from hTNF^{TG} animals from various time-points of age starting 4 weeks until 16 weeks after birth. Muscle weight and body weight were assessed from these animals. Muscle tissue, muscle weight and bodyweight from age and sex-matched wildtype animals served as controls. To investigate whether tumour necrosis factor (TNF) blockade protects hTNF^{TG} animals from muscle atrophy, 5 female hTNF^{TG} animals were treated with anti-TNF ab (Infliximab, 10mg/kg, 3x per week, ip). Untreated hTNF^{TG} animals served as controls. To identify proteolysis pathways and pro-inflammatory cytokine expression involved in muscle atrophy, the authors performed quantitative real-time PCR for Cathepsin L, B, S, H, D, MMP-9 and Interleukin (IL)-1 and IL-6 from mRNA isolated from muscle tissues of hTNF^{TG} and wildtype animals. To further investigate infiltration of inflammatory cells, muscle tissue sections are stained for macrophages, neutrophils, T cells and B cells and conventional hematoxylin/eosin.

Results The authors demonstrate that hTNF^{TG} mice show significantly less triceps surae muscle weight compared to sex- and age matched wildtype animals. Reductions in muscle weight became already manifest at the early age of 4 weeks and were continuously reduced until week 16. Due to decreased muscle weight, bodyweight was also significantly decreased in hTNF^{TG} animals compared to their wildtype littermates. The authors found a significantly increased mRNA expression levels of Cathepsin L, a lysosomal endopeptidase responsible for muscle protein degradation, in muscles from hTNF^{TG} compared to their wildtype littermates. In contrast, other proteases such as cathepsin B, S, H, D did not reach significantly increased expression levels between these 2 genotypes. Moreover, proinflammatory cytokines such as IL1 and IL6 are also significantly upregulated in muscles from hTNF^{TG} mice.

Conclusion Despite spontaneous development of chronic inflamed, erosive arthritis, chronic overexpression of TNF leads to skeletal muscle atrophy due to increased tissue-degrading cathepsin L in hTNF^{TG} animals.