SOCS3 is a novel bi-functional regulator of muscle growth and wasting

Andrea Bonetto[1,4], Andrea Camperi[2], Tufan Aydogdu[3], Marianne Pons[1], Ernie D. Au[1], Leonidas G. Koniaris[1], Teresa A. Zimmers[1,4]

[1]Department of Surgery, Indiana University School of Medicine, Indiana University-Purdue University Indianapolis, Indianapolis, IN. [2]Molecular Biotechnology Center, University of Torino, Italy. [3]Sanford-Burnham Medical Research Institute, La Jolla, CA. [4]Indiana University Simon Cancer center.

Disease states such as cancer and other inflammatory conditions often show elevated IL-6 levels that correlate with muscle wasting and mortality. Previously we reported that STAT3, a transcription factor downstream of IL-6 binding to its receptor, plays a causative role in cancer cachexia, and that STAT3 inhibition prevents muscle wasting. Others have also shown that STAT3 blockade rescues cachexia in a murine model of kidney failure. Altogether these results established STAT3 as a regulator of muscle mass. One of STAT3 downstream target genes is the Suppressor of cytokine signaling-3 (SOCS-3). Interestingly, SOCS3 has been reported to inhibit the IL-6/STAT3 signaling by means of a feedback mechanism. In particular, SOCS3 can prevent further STAT3 activation by inhibiting the activation of JAK kinases, competing for receptor binding motifs and targeting the receptor for proteasomal degradation. We thus sought to determine the role of SOCS3 in muscle growth regulation and whether SOCS3 can improve muscle wasting in conditions of high IL-6.

Adenoviral-mediated SOCS3 overexpression in C2C12 myotubes caused hypertrophy and rescued IL-6-induced myofiber shrinkage. Similarly, SOCS3 gene transfer in the tibialis muscle of tumor hosts and burn-injured mice prevented muscle atrophy due to elevated IL-6. We then generated MLC-SOCS3 transgenic mice overexpressing SOCS3 from a muscle-specific promoter. Interestingly, these animals exhibit a complex sexually dimorphic phenotype. Indeed, female mice showed higher SOCS3 protein levels in skeletal muscle compared to the males, consistently with decreased pSTAT3 expression. Despite reduced or unchanged body weights, the MLC-SOCS3 transgenics generally showed larger skeletal muscles compared to their wild-type littermates. 1-week-old and adult MLC-SOCS3 mice were also characterized by significantly larger muscle cross-sectional area. However, only adult male mice showed reduced number of muscle fibers and increased number of central nuclei, thus suggesting that SOCS3 could affect myogenesis and differentiation. On this line and consistent with previous reports, primary myoblasts isolated from MLC-SOCS3 mice were shown to proliferate at a lower rate and formed hypertrophic fibers upon differentiation. Furthermore, MLC-SOCS3 myotubes as well as C2C12 expressing SOCS3 were refractory to both catabolic (IL-6) and anabolic (IGF-1 and GH) stimuli.

These data suggest that SOCS3 could act as a bi-functional regulator of muscle growth, possibly by affecting differentiation and limiting both IL-6/STAT3-induced wasting as well as IGF-1/GH-associated signaling. Further investigation is needed to define whether SOCS3 may play a role in the activation of muscle satellite cells and to support the use of SOCS3 as a therapeutic approach in cachexia and sarcopenia.