

## Human sarcopenia reveals an increase in SOCS-3 and myostatin and a reduced efficiency of Akt phosphorylation

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Sarcopenia is the general term for a reduction in muscle quality and function due to aging. This is evidenced by muscle atrophy, particularly in fast type II fibres, which is related to the reduction of maximal voluntary strength (Deschenes, 2004). Sarcopenia has important socio-economic consequences since falls are a major source of morbidity and mortality in the increasing population of older adults (Mahoney *et al.*, 1994). We tested the hypothesis that sarcopenia in humans may be linked to increased levels of TNF $\alpha$  and SOCS3; the latter causing perturbations in growth hormone (GH) signalling and increasing myostatin (Liu *et al.* 2003). Consequently, this would result in a reduced phosphorylation and activation of Akt signalling (Morissette *et al.*, 2006) and therefore inhibit muscle hypertrophy and activate signalling cascades associated with muscle atrophy. The aims of the present study were to determine whether age-related sarcopenia in humans was linked with perturbations in TNF $\alpha$ , SOCS3, GH, STAT5 and IGF levels as well decreases in the Akt/GSK/mTOR and increases in the Akt/FKHR/atrogene signalling pathways.

This study investigated the regulation of several genes and proteins involved in the activation of key signalling pathways promoting muscle hypertrophy including GH/STAT5, IGF-1/Akt/GSK-3 $\beta$ /4E-BP1 and muscle atrophy including TNF $\alpha$ /SOCS3 and Akt/FKHR/atrogene, in muscle biopsies from 13 young (20 + 0.2 years) and 16 old (age, 70 + 0.3 years) males.

In old, when compared with the young subjects, type II muscle fibre cross sectional area was reduced by 40-45% and TNF $\alpha$  and SOCS-3 were increased by 2.8- and 1.5-fold, respectively. Growth hormone receptor (GHR) protein and IGF-1 mRNA were decreased by 45%. Total Akt, but not phosphorylated Akt, was increased by 2.5-fold and this corresponded to a 30% reduction in the efficiency of Akt phosphorylation in the older subjects. Phosphorylated and total GSK-3 $\beta$  was increased by 1.5- and 1.8-fold respectively, while 4E-BP1 levels were unchanged. Nuclear FKHR and FKHRL1 were decreased by 73% and 50%, respectively, with no changes in the atrophy target genes, atrogin-1 and MuRF1. Myostatin mRNA and protein levels were elevated by 2- and 1.4-fold, respectively.

This is the first study to compare the regulation of several key signalling pathways known to control skeletal muscle hypertrophy, including GH/STAT5, IGF-1/Akt/GSK/4E-BP1, and skeletal muscle atrophy, including TNF $\alpha$ /SOCS3 and Akt/FKHR/atrogene, in muscle biopsies from young and old men. Sarcopenia appears to be associated with an increase in TNF $\alpha$  and SOCS-3 which may result in a reduction of GHR levels or sensitivity. The increase in total Akt protein, but not in Akt phosphorylation, in muscle from the older subjects, suggests an inefficiency in Akt activation, and by analogy, reduced protein synthesis. The increase in myostatin mRNA and protein levels in the older subjects suggests that myostatin is a prime candidate inhibiting Akt phosphorylation in the elderly.

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