Age-related alterations in transforming growth factor-β (TGF-β) signalling in rat skeletal muscle: implications for sarcopenia

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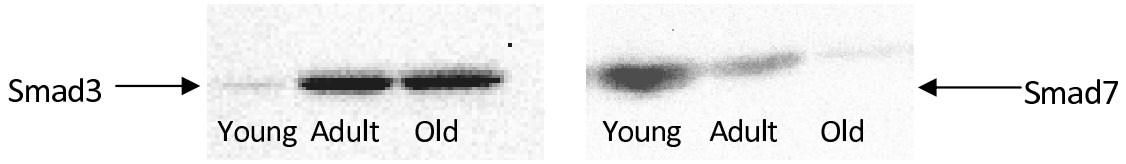
Ageing is associated with a progressive loss of muscle mass (sarcopenia) and strength. With Australia's demographic shifting towards an older population, and ageing already contributing significantly to our health care costs, sarcopenia is a major public health concern. Myostatin, a member of the transforming growth factor-β (TGF-β) superfamily, is a negative regulator of muscle mass and an age-related increase in myostatin expression (Léger *et al.,* 2008) is thought to contribute to sarcopenia. Whether the intracellular Smad signalling pathway tranducing the myostatin signal (and other TGF-β ligands) is altered with ageing is unknown. We tested the hypothesis that the protein abundance of Smad3 and Smad4, intracellular mediators of TGF-β signalling that translocate to the nucleus to suppress the transcription of muscle regulatory factors such as MyoD and myogenin, would be elevated in muscles aged; whereas protein abundance of Smad7, an inhibitory molecule that prevents the phosphorylation and nuclear translocation of Smad3/4, would be lower in muscles from aged compared with young rats.

Young (3 month, n = 5), adult (16 month, n = 5) and old (27 month, n = 5) F344 rats (Ryall *et al.,* 2007) were anaesthetised deeply (60 mg/kg sodium pentobarbitone, *i.p.*) and tibialis anterior (TA) muscles excised and analysed for the protein abundance (western blotting) of Smad3, Smad4 and Smad7.

TA muscles from adult and old rats had higher Smad3 protein abundance (by ~300 and ~400%, respectively) compared with young rats (the Figure). TA muscles of old rats also had lower Smad7 protein abundance (by ~80%), compared with young rats (the Figure). There was no difference in Smad4 protein abundance between age groups.



The findings raise important questions as to whether ageing is associated with alterations in the localisation of Smad3 and Smad7, and whether the lower Smad7 protein abundance in the TA of old rats involves: i) reduced Smad7 acetylation; ii) increased association with histone deactylase 1 (HDAC1), resulting in Smad7 deactylation; or iii) increased association with Smurf1, leading to Smad7 ubiquination.

This study revealed that in rats, ageing is associated with an enhanced Smad3 protein abundance and a corresponding reduction in protein abundance of the inhibitory Smad7. These findings implicate increased TGF-β superfamily signalling in the negative regulation of muscle mass and ultimately, to age-related muscle wasting and weakness. A better understanding of the cellular mechanisms underlying sarcopenia may lead to potential therapeutic strategies to attenuate sarcopenia.

Léger B, Derave W, De Bock K, Hespel P, Russell AP. (2008) *Rejuvination Research*, **11:** 163-175B.
Ryall JG, Schertzer JD, Lynch GS. (2007) *Journal of Gerontology: Biological Sciences*, **62:** 813-23.

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