Targeting activin to counteract muscle wasting and cachexia

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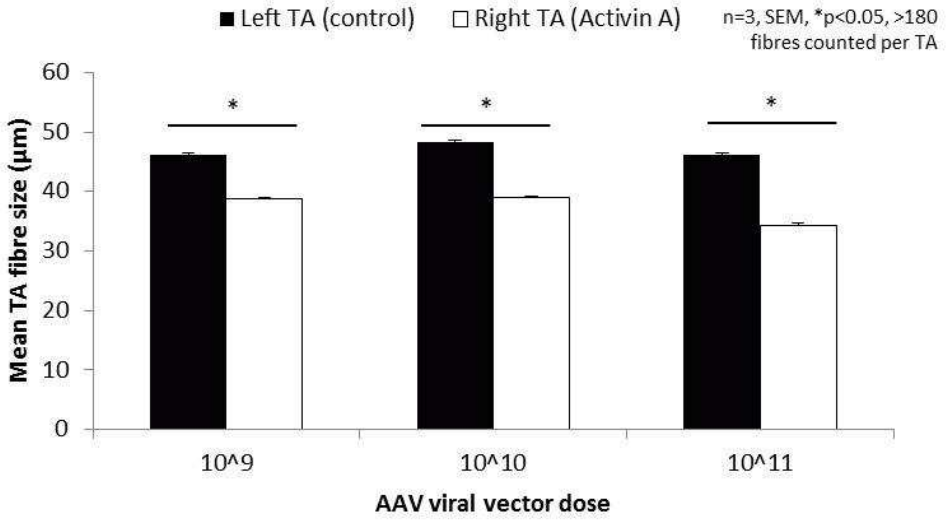
Cachexia is a debilitating secondary wasting syndrome that occurs in patients suffering from major disease, such as cancer, AIDS and heart failure. Muscle loss is the most debilitating aspect, but this syndrome is also characterized by anaemia, anorexia and extreme fatigue. In patients with advanced cancer, 80% will also present with cachexia, and nearly 30% of these patients die from the wasting effects of cachexia rather than the cancer itself (Tisdale, 2009). The problem is that not much is known about what causes cachexia, so treatment options are limited. Recent evidence suggests that signalling through the activin type II receptor (ActRIIB) plays a dominant role in the aetiology of cachexia (Zhou *et al.*, 2010). ActRIIB mediates the signalling of a subset of transforming growth factor-β (TGF-β) ligands, including myostatin, activin A, activin B and GDF-11. In multiple cancer cachexia models, pharmacological blockade of the ActRIIB pathway not only prevented further muscle wasting, but restored previous muscle loss. In a screen of human cancer cell lines, we found that activin A was highly expressed in several aggressive or metastatic cells. To show a causal link between increased systemic activin A and muscle wasting, we utilized adeno-associated viral vectors (AAV) to express activin A in the right hindlimb tibialis anterior (TA) muscle of isoflurane gas-anaesthetized 6-8 week-old male C57Bl/6 mice; the left TA muscle was injected with an empty AAV as a control. Increasing viral doses (109 – 2x1011) resulted in a rapid, dose-dependent decrease in the mass of the injected TA muscle. After 4 weeks, there was a significant reduction in muscle fibre size and function (Figure).



Western blot analysis indicated that activin A increased the phosphorylation of the transcription factor SMAD3 and correlated with dephosphorylation of Akt, p70S6K and S6RP, suggesting inhibition of the protein synthesis pathway. Concomitantly, qPCR analysis indicated an upregulation of atrogin-1 and MuRF-1 transcripts, two key ubiquitin ligases that regulate protein degradation. At the higher viral doses, hindlimb muscles surrounding the TA also decreased in mass and size. In these mice, circulating activin A levels increased up to 12-fold and caused significant decreases in liver, testes and total body mass. Our findings demonstrate the importance of blocking activin A activity in cachexia and, to this end, we have recently developed the first specific activin A antagonist. *In vivo*, this antagonist completely prevented activin-induced muscle wasting in C57Bl/6 mice. Current studies are evaluating the efficacy of the activin antagonist to reverse muscle wasting in a murine model of cancer cachexia.

Zhou X, Wang JL, Lu J, Song Y, Kwak KS, Jiao Q, Rosenfeld R, Chen Q, Boone T, Simonet WS, Lacey DL, Goldberg AL, Han HQ. (2010) Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* **142:** 531-43.

Tisdale MJ. (2009) Mechanisms of cancer cachexia. *Physiological Reviews* **89:** 381-410.