Activin-$\beta_c$ abolishes cancer-associated cachexia in inhibin-deficient mice

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Cancer cachexia

Clinical management of cachexia is currently both limited and complex.

Cachexia remains a challenging clinical syndrome, the importance of which lies in its prevalence and profound adverse effect on patients’ quality and length of life.

The optimal treatment of cancer cachexia remains unknown.
Activins belong to the TGF-β superfamily

Activins were originally purified from gonadal fluid as glycoproteins that stimulated the FSH (follicle stimulating-hormone) release from the pituitary gland

Activin A is a major form of the activins

Beyond its classic role in reproductive biology activin A also function as paracrine/autocrine factor in non-gonadal tissues, including skeletal and heart muscles.
Activin A role in the pathogenesis of wasting: the INHAKO mouse model

Matzuk et al. 1994
Activin antagonism as an emerging target for therapeutic interventions

Schematic representation of activin signalling and its control by antagonists

Marino et al. 2013
A novel Activin A antagonist: Activin-βC

Metabolic, Endocrine and Genitourinary Pathobiology

Activin C Antagonizes Activin A in Vitro and Overexpression Leads to Pathologies in Vivo

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Gold et al. 2009
Aim of the study

Is Activin-βC overexpression having an effect on the onset of gonadal tumours and cancer associated cachexia?
Materials and methods

• Human activin-C (under the control of a CMV promoter)- overexpressing mice were produced by standard methods.

• ActC++ mice were crossed with heterozygous α-KO and sacrificed at 8 weeks

• Testis and ovaries % tumour was assessed based on the Cavalieri principle

• Smad-2 were estimated based on a method that allowed unbiased semi-quantitation of the percentage of positive cells

• Activin-A levels in serum assess by ELISA

• Statistics: groups compared using ANOVA and survival curves analysed with the Mantel-Cox log-rank test
RESULTS
1) Overexpression of activin-βC abolishes severe weight loss and prolongs survival.

*\( p<0.05 \) in \( n=8–11 \) mice per group. (A), (B) ANOVA and a Bonferroni post-hoc test. (C) Male and (D) female Kaplan–Meier survival plots.
2) Overexpression of activin-βC modulates gonadal tumour development
3) Elevated activin-A and Smad-2 phosphorylation evident in α-KO mice is significantly reduced by activin-βC overexpression.

Activin-A homodimer assessed by ELISA in the serum (A). Values represent mean±SEM in n=8 WT, 6 α-KO, and 7 α-KO/ActC++. ***p<0.001, *p<0.05 versus WT littermate controls; ANOVA with a Bonferroni post-hoc test. SDS-PAGE and western blot analysis of phosphorylated Smad-2 relative to totalSmad-2 in the testis, (B) Values represent mean±SEM in n=5 mice per group assessed in duplicate. **p<0.01, *p<0.05 versus WT littermate controls; ANOVA with a Bonferroni post-hoc test.
Conclusion

1. *Activin-βC antagonizes Activin A in vivo (INHAKO mouse model)*

- Abrogates sex cord stromal tumours progression
- Abolishes cancer associated-weight loss
- Increases survival

2. *Our study suggests that the activin signalling pathway might be a therapeutic target for reversing weight loss in cancer cachexia and potentially other catabolic conditions such as neuromuscular and muscoskeletal disorders*
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Treatment with activin receptor antagonists (follistatin, sActRII, activin C) leads to decreased activin signalling, thereby preventing muscular atrophy, cancer associated-weight loss and modulating gonadal tumour phenotype in the inhibin a-KO mouse.
A SINGLE ASCENDING-DOSE STUDY OF MUSCLE REGULATOR ACE-031 IN HEALTHY VOLUNTEERS

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ABSTRACT: Introduction: ACE-031 is a soluble form of activin receptor type IIB (ActRIIB). ACE-031 promotes muscle growth by binding to myostatin and other negative regulators of muscle mass. Methods: This double-blind, placebo-controlled study evaluated the safety, pharmacokinetics, and pharmacodynamics of ACE-031 in 48 healthy, postmenopausal women randomized to receive 1 dose of ACE-031 (0.02–3 mg/kg SC) or placebo (3:1). Results: ACE-031 was generally well-tolerated. Adverse events included injection site erythema. Mean ACE-031 AUC0–∞ and Cmax increased linearly with dose; mean T1/2 was 10–15 days. Statistically significant increases in mean total body lean mass (3.3%; P = 0.03, by DXA) and thigh muscle volume (5.1%; P = 0.03, by MRI) were observed at day 29 in the 3 mg/kg group. Statistically significant changes in serum biomarkers suggest ACE-031 also improved bone and fat metabolism. Conclusions: Single-dose ACE-031 treatment was generally well-tolerated and resulted in increases in muscle mass in healthy postmenopausal women.

Muscle Nerve 000: 000–000, 2012
TGF-Inhibitors in Clinical Practice

AP-12009 directed against the mRNA of TGF-b represents an example of a large molecule inhibitors

This molecule has been used in phase I/II studies in advanced pancreatic carcinoma, metastatic melanoma and metastatic colorectal carcinoma. A study using AP-12009 in high-grade glioma patients showed a significant survival benefit compared to standard chemotherapy treatment.