Exploring new targets within the TGFβ signaling network as interventions for cachexia

P. Gregorevic, Baker IDI Heart and Diabetes Institute, PO Box 6492, Melbourne, VIC 3004, Australia.

Transforming growth factor-β (TGFβ) superfamily proteins that signal *via* activin type II receptors (ActRII), including activin A, activin B, myostatin and GDF11, are central regulators of tissue homeostasis. More recently, increased circulating levels of key ActRII ligands have been implicated in promoting the loss of lean and fat mass associated with conditions in which cachexia is observed. Blocking the activity of ActRII ligands *via* administration of soluble forms of ActRII has been shown to protect against muscle wasting in cachexia models, but can exert effects in other tissues and organ systems due to the pleiotropic nature of ActRII ligands. Thus, while these results are exciting, the application of soluble ActRII interventions has been limited, and highlights a need to explore the development of new reagents that target the effects of ActRII ligands.

Here, we present data on new strategies for targeting the TGFβ signalling network, as prospective interventions for cachexia. Firstly, as activin A and activin B can induce a cachectic phenotype, we have developed modified activin A and activin B prodomains that function as specific activin antagonists. We have established that administration of these novel reagents *via* gene delivery or protein treatment is protective in mouse models of activin-induced wasting, and can increase muscle mass in healthy mice, whilst avoiding the comparatively broad ligand tropism of soluble ActRII. Secondly, we have developed gene-delivery based approaches to limit ActRII-mediated signalling within skeletal and cardiac musculature that avoid targeting ligands at the extra cellular level. Local and systemic administration of interventions that inhibit ActRII-mediated signalling *via* enhanced expression of inhibitory Smad proteins achieved marked conservation of skeletal and cardiac muscle mass in mice bearing cachexia-inducing tumors. Finally, we have found that increasing the expression of specific TGFβ family ligands can antagonise ActRII-mediated signalling, and afford protection from features of cachexia caused by ActRII ligands, or implantation of cachexia-inducing tumors.

Combined, these studies introduce new strategies for preventing and reversing features of frailty associated with cachetic conditions. Our communication will explore the mechanisms of action underlying these intervention strategies, and consider therapeutic utility in relation to the prevention and treatment of cachexia.