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Links between the IGF-1 signalling pathways and skeletal muscle hypertrophy in sheep

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Meat yield and product quality are important to the Australian sheep industry particularly as the country faces increased competition from imported meats. The *Callipyge* genotype in sheep is a natural mutation of chromosome 18 that leads to significantly greater muscle yield (Cockett and Jackson, 1994). However the *Callipyge* phenotype is not expressed until 4 to 6 weeks of age (Jackson et al., 1997). The *Carwell* genotype of Poll Dorset sheep is another natural polymorphism that leads to greater meat yield, though neither the genetic polymorphism nor the biochemical mechanism is known. Whilst increase in muscle yield may be beneficial for the consumption market, the mechanism underlying hypertrophy in these genetic variants is not fully understood.

Previous studies have shown that IGF-1 (insulin like growth factor) induces skeletal muscle hypertrophy by stimulating the phosphatidylinositol 3-kinase-Akt-mTOR and Ras-Raf-MEK-ERK pathways (Glass, 2003). This induction is characterized by an increase in size of muscle fibres (hypertrophy) rather than number (hyperplasia), resulting in an enhanced rate of protein synthesis (Glass, 2003 and Foulstone and Huser, 2004). The literature suggests that IGF-1 is capable of inducing skeletal hypertrophy in human and mouse muscle in vivo. In vitro studies also suggest that IGF-1 might induce skeletal myocyte hypertrophy through the calcineurin-mediated signalling pathway via mechanisms involving GATA-2 and NF-ATc1. (Musaro et al., 1999).Thus it is essential to elucidate the link between the metabolic networks and the signalling pathways that influence skeletal muscle hypertrophy.

The aim of this research is to use knowledge of muscle development in mouse and human to help understand development in sheep, particularly in the sheep muscle genetic variants *Callipyge* and *Carwell*. We will examine integral components of the IGF-1 signaling pathways to determine if they are associated with the hypertrophic growth observed in these genetic variants. Western blotting will be used to examine the activity, and phosphorylation status of PI3 kinase, Akt, mTOR, calcineurin and p70S6K. This study will develop in vitro models for hypertrophy based on primary sheep cultures derived from genetic variants associated with increased meat yield. This will lead to greater understanding of the molecular mechanisms and biochemistry governing increased muscle yield in these phenotypes. Moreover, we will learn about the link between hypertrophy and the toughness of these mutations in sheep.

Our results show that IGF-1 treatment results in hypertrophy in vitro of C_2C_{12} (mouse muscle line) and sheep primary myotubes. Hypertrophy in response to human recombinant IGF-1 was measured as an increase in number of DAPI-stained nuclei within desmin positive cells (4–5 per myotube); increased creatine kinase per unit cellular protein (2-fold) and increased expression of mTOR and p70S6K (2–3- fold protein measured by densitometry).

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