A mouse model for polar overdominance?

Pirottin D., Takeda H., Tamma N., Delcombel R., Georges M., Charlier C.

The callipyge mutation (CLPG) is responsible of a muscular hypertrophy phenotype in sheep and is characterized by a particular mode of inheritance, called polar overdominance, where only heterozygous individuals having received a paternal mutation exhibit the muscular hypertrophy.

The CLPG mutation has been mapped to the *DLK1-GTL2* imprinted domain and is an A to G transition in a 12-bp motif, conserved between Eutherian mammals and located in the middle of the *DLK1-GTL2* intergenic (IG) region.

We have previously demonstrated that the mutation (i) invalidates a long-range regulatory element shared by genes belonging to the central part of the domain, resulting in ectopic post-natal expression of those genes in skeletal muscle and (ii) alters the muscular epigenotype of the *DLK1-GTL2* IG region, including a strongly enhanced bidirectional long-range IG transcription.

The muscular hypertrophy phenotype is due to the lack of repression of paternally expressed genes (DLK1 and/or PEG11) in skeletal muscle, while it has been suggested that the observed polar overdominance phenomenon could be the result of a *trans*-inhibition of the paternally expressed genes mediated by the maternally expressed non-coding RNAs.

A mouse model recapitulating this polar overdominance phenomenon is essential for the detailed analysis of its molecular basis. For that purpose, two transgenic lines have been produced by homologous recombination in ES cells. The first line corresponds to a knock-in of the point mutation (A>G) and the second is harbouring a deletion of the conserved 12-bp motif (Δ12).

A detailed spatio-temporal expression profile of the genes orthologous to the ones affected by the CLPG mutation in sheep is underway in mice from the four genotypes at the mutated locus, for both transgenic lines. Results indicate that the molecular features observed in sheep are only partially reproduced in the two mouse models.