Maternal Myostatin Deficiency Modulates Placental Gene Expression and Signaling Pathways

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Introduction: Intrauterine growth restriction (IUGR) affects approximately 9% of pregnancies, and is associated with adverse outcomes like preterm birth and stillbirth. IUGR also poses risks for long-term health effects, including musculoskeletal deficiencies, obesity, and insulin resistance in adulthood. Placental insufficiency is a major contributor to IUGR. Myostatin acts as a negative regulator of muscle development. Our previous research revealed that Wildtype (WT) fetuses carried by myostatin deficient dams (*Mstn*+/-) exhibited 25% higher weight than WT offspring from WT dams, alongside increased muscle mass and bone strength in adulthood. Notably fetal myostatin concentrations were unaffected. Metabolomics analysis highlighted differences in amino acids and lipopolysaccharides in serum of fetuses from *Mstn*+/- dams. Moreover, WT placentas from myostatin deficient dams displayed larger labyrinth and junctional zone areas. This study aims to investigate the impact of maternal myostatin reduction on gene expression.

Experimental Design: We performed reciprocal crosses of WT and $Mstn^{+/-}$ parents with WT dams serving as controls for the $Mstn^{+/-}$dams. Placentas were collected at E17.5 day of pregnancy. Total RNA was extracted from five male and five female WT placentas from each cross and submitted for sequencing. Read counts were aligned and DEseq2 was used to identify differentially expressed genes.

Results: There were 297ifferentially expressed genes between the two maternal genotypes (adj. p-value <0.05). There were 44 transcripts upregulated at least 15-fold in the placentas from a myostatin-deficient mother compared to those from a WT mother. These include *Dsg3*, *Marco*, *Acod1*, *Il1b*, *Retnlg* and *Hp* which all part of the inflammatory response pathway, the most upregulated pathway overall. There also significant upregulation of transcripts for *Gpr132*, *Gpr84*, *Rnd1*, *Plcd1,* all members of signal transduction pathways.

Conclusion: These results suggest that maternal myostatin reduction may affect offspring growth in part by altering placental signaling through both inflammatory and growth factor signaling pathways.