Placental expression of myostatin and follistatin-like-3 protein in a model of developmental programming

Hassendrini N. Peiris,1* Anna P. Ponnampalam,1* Claire C. Osepchook,1 Murray D. Mitchell,1 and Mark P. Green1,2

1The Liggins Institute and National Research Centre for Growth and Development, University of Auckland, Auckland; and 2AgResearch, Ruakura Research Centre, Hamilton, New Zealand

Submitted 9 November 2009; accepted in final form 20 January 2010

Placental expression of myostatin and follistatin-like-3 protein in a model of developmental programming. Am J Physiol Endocrinol Metab 298: E854–E861, 2010. First published January 26, 2010; doi:10.1152/ajpendo.00673.2009.—Maternal undernutrition during gestation is essential to prevent and/or develop treatments for the effects of aberrant nutrition, nutrient transfer, and detrimental changes to fetal development. A potential role for myostatin as a mediator of nutrient uptake and transport from the mother to the fetus was shown through the recent finding that myostatin acts within the human placenta to modulate glucose uptake and therefore homeostasis. The mRNA and protein expression of myostatin and its inhibitor, follistatin-like-3 (FSTL3), was studied in the placenta and skeletal muscle of a transgenerational Wistar rat model of gestational maternal undernutrition in which the F2 offspring postweaning consumed a high-fat (HF) diet. Alterations in placental characteristics and offspring phenotype, specifically glucose homeostasis, were evident in the transgenerationally undernourished (UNAD) group. Myostatin and FSTL3 protein expression were also higher (P < 0.05) in the placenta of the UNAD compared with the control group. At maturity, UNAD HF-fed animals had higher (P < 0.05) skeletal muscle expression of FSTL3 than control animals. In summary, maternal undernutrition during gestation results in the aberrant regulation of myostatin and FSTL3 in the placenta and skeletal muscle of subsequent generations. Myostatin, through the disruption of maternal nutrient supply to the fetus, may thus be a potential mediator of offspring phenotype.

undernutrition; placenta; muscle; growth differentiating factor-8; transgenerational

MYOSTATIN, initially designated as growth differentiating factor-8, is a distinctive member of the transforming growth factor-β superfamily (26, 27). Many of the characteristic features found within the transforming growth factor-β superfamily exist in myostatin. This protein is highly conserved across a number of different species, and the functional importance of myostatin can be inferred from the preservation of sequence homology seen across species (22, 35). McPherron et al. (26) first demonstrated through gene targeting techniques that disrupted the function of the myostatin gene in mice that myostatin acts as a negative regulator of muscle development and that this disruption resulted in a two- to threefold increase in muscle mass.

Further studies have identified this action to occur through proteolytic cleavage of the myostatin precursor protein (52 kDa) that is proteolytically cleaved twice to release the biologically mature form of myostatin (~12 kDa) (19, 20, 25). Both the unprocessed and mature forms of myostatin are capable of forming disulfide-linked dimers. However, the active form of myostatin (~28 kDa) arises only from a dimer of the mature myostatin protein (20, 35). Once active, the myostatin dimer binds to its receptor activin receptor IIB (ActRIIB) to initiate the Smad-mediated signaling pathway that eventually results in the transcription and expression of genes needed to mediate the negative regulation of muscle development (20, 22).

The expression and activity of myostatin is regulated by a number of proteins, including the myostatin propeptide (latency-associated peptide), growth and differentiation factor-associated serum protein-1, and follistatin, all of which are known to prevent the binding of myostatin to its receptor ActRIIB (1, 35). However, the most potent regulator of myostatin is follistatin-like-3 (FSTL3) (1), which is known to bind myostatin in serum to prevent the association of myostatin with its receptor (36). Further regulation by FSTL3 is also hypothesized through the dissociation of myostatin from its receptor, with FSTL3 instead remaining bound to myostatin postdisassociation, thus inhibiting myostatin activity (17, 22).

Recently, myostatin has also been shown to be crucial for modulation of glucose homeostasis and adipogenesis (11, 45). Wider functions of myostatin are supported by the discovery of myostatin expression in a number of different tissues, including brain (35), mammary (23), cardiac (39), adipose (28), endometrium (38), and human placenta (29). One particularly interesting finding is the changing myostatin expression throughout gestation in the human placenta. Mitchell et al. (29) have shown that there is a negative correlation in human placenta between myostatin expression and gestational age, with a higher myostatin expression evident in preterm human placental tissues compared with term placental tissues. Additional in vitro studies also found that myostatin regulates glucose uptake in human placenta (3, 29).

The placenta, as a conduit between mother and fetus, influences the intrauterine growth and development of the fetus through regulating the supply of oxygen, hormones, and nutrients (12). Therefore, the in utero nutritional environment is fundamental to the programming of the fetus for life outside the womb (5, 14). Any changes to the function of the placenta due to environmental cues, such as an altered maternal nutritional state, can thus influence the intrauterine growth and developmental programming of the fetus (5, 14). Interestingly, both under- and overnutrition of mothers during gestation are
widely linked to unfavorable changes in fetal development, leading to the propensity for metabolic disorders and obesity later in adult life (6–8, 14, 41). Perhaps more importantly, the effects of fetal programming are not only observed in the immediate generation but also identified in subsequent generations (9). Consequently, focus has been upon the discovery of methods to prevent and alleviate detrimental effects of aberrant gestational nutrition, although to date, few if any methods have been identified. Therefore, understanding the mediators and physiological processes involved in the placental transport of nutrients to the fetus is the first critical step in identifying potential methods. One such mediator, through its ability to modulate glucose homeostasis, may be the expression of placental myostatin.

The aim of this study was to utilize a model of transgenerational maternal undernutrition to investigate the changes in the expression of myostatin and its inhibitor FSTL3 in rat placenta and in skeletal muscle. The ultimate aim was to investigate whether changes in placental myostatin expression relate to the embryonic and adult phenotypes.

**METHODS AND MATERIALS**

**Animal model and measurements.** The animal model depicted (Fig. 1) was based upon an established model of undernutrition (41, 42, 44). Briefly, virgin female Wistar rats (F0 generation) were reared on an ad libitum standard chow diet (18% protein, 5% fat; 2018 Teklad Global Rodent Diet) and mated at 120 ± 5 days of age with males also fed an ad libitum standard chow diet. Following confirmation of mating, the females were individually housed and received either a standard chow diet ad libitum (AD group) or 30% of the AD chow diet (UN group) throughout gestation. Dams in both groups were fed chow ad libitum during lactation. Litter size was standardized on day 1 to 10 pups/litter to standardize nutrition until weaning. Female offspring from these pregnancies (F1 generation) were weaned and fed chow ad libitum until 120 ± 5 days of age before being mated with AD males and fed one of the two dietary regimes described (AD or UN) during gestation. This produced three groups [control (ADAD), undernourished (ADUN), and transgenerationally undernourished (UNAD)]; a UNUN group was not able to be included for ethical reasons. Female fetuses and offspring of these pregnancies are then F2 generation and are the subjects of this study.

A subcohort of these pregnancies (F1 dams with F2 fetuses) were culled from each group at embryonic day 20 (E20) with maternal, fetal, and placental parameters recorded. Fetal skeletal muscle samples were collected from the hind leg quadriceps and placental tissues were collected, snap-frozen, and stored at −80°C. When the remaining F1 females gave birth, litter size and pup sex were recorded before litter size was standardized on day 1 to 10 pups, five males and five females where possible. All these F2 pups were nursed by their own dams, which were fed chow ad libitum until weaning (day 22). At weaning F2 males were removed, and only F2 females were studied to maturity, with one-half of these offspring from each of the three F0 and F1 nutritional groups then fed either a chow or high-fat (65% kcal as fat; D12492 Research Diets) diet ad libitum until being euthanized at day 140. The body weights of F2 females were recorded from birth every 3 days until day 40 and then every 5 days until day 140. On day 130, body measurements and composition were determined in these females (n = 10 per diet per group) by dual-energy X-ray absorptiometry (DEXA) using a LUNAR Prodigy Scanner (GE Medical Systems) (42). On day 140, after an overnight fast, the animals were euthanized via decapitation under pentobarbital sodium anesthesia (60 mg/kg ip). Blood was collected into heparinized vacutainers, kept on ice, centrifuged for 15 min at 1,500 × g and stored at −20°C for further analysis. Skeletal muscle samples were collected from the left hindleg quadriceps and snap-frozen and stored at −80°C. All animal procedures undertaken were approved by the University of Auckland Animal Ethics Committee.

**Plasma assays.** Plasma glucose was measured along with quality controls using commercial kits (Roche Diagnostics) on an autoanalyzer (Roche/Hitachi 902 Analyzer; Hitachi, Tokyo, Japan). Plasma insulin was determined by a rat insulin ELISA (Mercodia, Uppsala, Sweden), following the manufacturers’ instructions. The insulin assay sensitivity (assay n = 6) was 0.07 μg/L, and the intra- and interassay coefficients of variation were 3.4 and 6.3%, respectively.

**RNA extraction.** Total RNA was extracted using Trizol reagent (Invitrogen Life Technologies, Auckland, New Zealand) according to protocol by Ponnampalam and Rogers (31). Briefly, frozen placental samples were powdered using a pestle and mortar, cooled with liquid nitrogen, homogenized in 1 ml of Trizol, and incubated at room temperature for 5 min. After the addition of chloroform (0.2× volume of Trizol), the samples were incubated for another 3 min at room temperature and centrifuged for 15 min at 12,000 g (4°C), and the aqueous-phase RNA was separated from DNA/protein fraction, mixed with 400 μl of isopropanol, and incubated at room temperature for 20 min. This was followed by centrifugation for 10 min at 12,000 g (4°C). The RNA pellet was washed twice with 75% ethanol followed by centrifugation for 6 min at 10,000 g (4°C). RNA was resuspended in RNase-free water. To eliminate potential genomic DNA contamination, RNA samples were treated with RNase-free DNase (Invitrogen Life Technologies) according to the manufacturer’s instructions. After the DNase treatment, RNA was purified by storing overnight at −20°C in two volumes of 100% ethanol and 0.1 volume of 3 M sodium acetate. RNA was centrifuged at 12,000 g for 40 min at 4°C, the pellet was washed twice with 70% ethanol, and then the RNA was resuspended in RNase-free water. RNA concentration was quantified using NanoDrop ND-1000 spectrophotometer (NanoDrop Products). All RNA samples were stored at −80°C until required. Each RNA sample (2.5 μg) was reverse transcribed using Superscript III according to the manufacturer’s protocol (Invitrogen Life Technologies).

**Quantitative real-time PCR.** Quantitative real-time PCR was performed using the ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems, Auckland, New Zealand), SYBR Green Master Mix (Applied Biosystems), and the primer sequences shown in Table 1. Running conditions were the same for all genes. Enzyme activation was 95°C for 20 s, denature was 95°C for 3 s, and annealing/extension was 60°C for 40 cycles, followed by melting curve analysis. Relative
mRNA expression was determined by the measurement against a specific cDNA standard. Each sample was run in duplicate, and hypoxanthine phosphoribosyltransferase was used as a housekeeping gene and to normalize all results against.

**Protein extraction.** Frozen muscle and placental samples (50–100 mg) were powdered using a pestle and mortar cooled with liquid nitrogen to prevent thawing. Samples were then sonicated (Bandelin Electronic, Berlin, Germany) with a 10 × 1 s pulse (0.2 s of a homogenizing pulse, 0.8 s resting) at 40% power in RIPA buffer [20 mM, pH 7.4–7.6, Tris, 1% Triton base, 10% deoxycholic acid, 500 mM EDTA, 1% sodium dodecyl sulphate, and a protease inhibitor tablet (Roche Applied Science, Wellington, New Zealand)] and centrifuged at 25,200 g at 4°C for 15 min. The supernatant was stored at −80°C, and total protein concentration was determined using BSA serially diluted standards using a bicinchoninic assay (Sigma-Aldrich, Castle Hill, Australia).

**Western blot analysis.** All reagents used were purchased from Invitrogen Life Technologies, unless stated otherwise. For use in the NuPage BIS-TRIS Electrophoresis System. Total protein extracted from placental tissue (30 μg) was mixed with 20× reducing agent (DTT; Sigma-Aldrich) and 4× loading buffer (NuPage LDS sample buffer) and placed for 10 min in a 70°C heating block. Reduced proteins were loaded and separated in NuPage 4–12% Bis-Tris Precast Gels for 1 h at 200 V and transferred (NuPage Transfer buffer) onto a polyvinylidene fluoride membrane for 2 h at 50 V. The membrane was stained with Ponceau S for protein transfer verification, and gels were terminally stained with Cooamassie blue. Membranes were blocked for 1 h in 1% blocking solution (1 g of nonfat milk powder in 100 ml of PBST) for myostatin, 2% blocking solution (2 g nonfat milk powder in 100 ml of PBST) for FSTL3 incubated overnight at 4°C in primary antibody, 1:3,000 dilution for myostatin [goat polyclonal growth differentiating factor-8 (F-13), Sc-34781; Santa Cruz Biotechnology, Santa Cruz, CA], and 1:5,000 dilution for FSTL3 [goat polyclonal FLRG (N-18), Sc-21302; Santa Cruz Biotechnology]. All membranes were incubated for 2 h in 1:10,000 dilution secondary antibody (polyclonal rabbit anti-IgG-HRP; Santa Cruz Biotechnology). SuperSignal West Dura Extended Duration substrate (Pierce Global Science & Technology, Auckland, New Zealand) was used to visualize the proteins on Agfa medical X-ray blue film and developed using a Kodak X-OMAT 1000 automatic X-ray film processor. Relative optical densities of the bands were determined using a GS 800 calibrated densitometer and analyzed using Quantity One software (Bio-Rad Laboratories, Auckland, New Zealand). The relative optical densities were normalized to sheep muscle expression of myostatin and FSTL3 protein.

**Statistical analysis.** All analyses were run using a general linear mixed model (43) followed by Tukey’s post hoc comparison performed on SAS software version 9.1 (SAS Institute, Cary, NC). Differences in F2 female variables (weight and body composition), plasma metabolite concentrations, and the relative expression of myostatin and FSTL3 in skeletal muscle and placenta were analyzed with group and diet included in the model where appropriate, and all interactions between the main effects were analyzed. E20 fetal and placental weights, as well as the fetal-to-placental ratio (individual and total), were also analyzed by one-way ANOVA. All data presented are as means ± SE.

**RESULTS**

**E20 fetus, placenta, and fetus-to-placenta ratio.** ADUN fetuses were lighter (P < 0.001) than both UNAD and ADAD fetuses (Fig. 2). Moreover, placental weights differed (P < 0.001) between all three groups. Placentae of UNAD pups were smaller (P < 0.05) than ADAD placentae. Consequently, the placenta-to-fetus ratio also differed between groups, with the UNAD fetus-to-placenta ratio being equivalent to that of the ADUN rather than ADAD group, which had a higher (P < 0.001) fetus-to-placenta ratio than the other two groups (Fig. 2).

**Day 130 body composition and day 140 weight and plasma metabolite concentrations.** Gestational as well as postnatal diet was found to affect the body weight, body composition, and plasma metabolite concentrations of F2 females. DEXA analysis of the F2 generation female offspring at day 130 of age identified a higher (P < 0.0001) body fat percentage in the females fed a high-fat diet compared with their Chow-fed contemporaries. Within the high-fat-fed group, the ADUN and UNAD females had a significantly (P < 0.05) lower body fat percentage compared with the ADAD females (Fig. 3). The percentage of total lean muscle in the ADAD high-fat-fed females was higher (P < 0.05) compared with the Chow-fed ADAD and UNAD females as well as both the Chow- and high-fat-fed ADUN females. In a further comparison of the fat-to-lean ratio, it was observed that the ADAD high-fat-fed females had a higher (P < 0.05) fat-to-lean ratio compared with all of the other groups (data not shown). At day 140 in the F2 generation, female body weight data followed a pattern similar to that of the body fat percentage since the females fed a high-fat diet were heavier (P < 0.0001) than those fed the Chow diet. The UNAD high-fat-fed females were heavier (P < 0.05) than the ADUN females, and both of these groups had a lower (P < 0.05) body weight compared with the ADAD high-fat-fed females (Fig. 3). Interestingly, plasma glucose concentrations analyzed at day 140 were found to be significantly higher (P < 0.05) in the UNAD females fed a high-fat diet compared with all other groups (Fig. 3). Plasma insulin concentrations were also elevated (P < 0.0001) by the feeding of a high-fat diet, although this was evident only in the ADUN and UNAD groups, not the ADAD group. No difference between groups or group × diet interaction was identified (data not shown).

**E20 placental tissue expression of myostatin and FSTL3.** Real-time quantitative PCR analysis for the mRNA expression of myostatin and FSTL3 within the placental tissues found a trend toward a higher expression for both proteins in the
UNAD placental tissues; however, significance ($P < 0.05$) was not reached (Fig. 4).

Western blot analysis of the E20 placental tissues identified the protein expression myostatin to be higher ($P < 0.05$) in the

UNAD placental tissues; however, significance ($P < 0.05$) was not reached (Fig. 4).

Western blot analysis of the E20 placental tissues identified the protein expression myostatin to be higher ($P < 0.05$) in the
UNAD group compared with the placental tissues of both the ADAD and ADUN groups (Fig. 4). FSTL3 protein expression followed a pattern similar to myostatin. The UNAD placental tissues had a higher \((P < 0.05)\) protein expression of FSTL3 compared with both the ADAD and ADUN placental tissues (Fig. 4).

**Skeletal muscle tissue expression of myostatin and FSTL3 (E20 and day 140).** Western blot analysis of the E20 skeletal muscle tissues found the protein expression of myostatin to be lower \((P < 0.05)\) in the UNAD group compared with the muscle tissues of both the ADAD and ADUN groups (Fig. 5). No differences in the FSTL3 expression of E20 skeletal muscle were identified (data not shown).

The day 140 female skeletal muscle tissues of the ADAD, ADUN, and UNAD groups were investigated by group and postnatal diet (chow or high fat). No differences in myostatin expression between diets within groups or between groups were identified, although the high-fat-fed UNAD group tended \((P = 0.09)\) to have a decreased expression of the myostatin dimer compared with the UNAD chow-fed group (Fig. 5). FSTL3 expression differed only between high-fat but not Chow-fed groups, as FSTL3 expression in the UNAD high-fat-fed group was higher \((P < 0.05)\) than in both other high-fat-fed groups and all three Chow-fed groups (Fig. 5).

**DISCUSSION**

This study shows for the first time that the expression of myostatin and FSTL3 in the placenta and skeletal muscle of F2 offspring is altered significantly in response to transgenerational undernutrition. Moreover, altered expression of these proteins is associated with aberrant plasma metabolite regulation and attenuated body fat deposition in the mature female offspring in response to a postnatal high-fat diet.

In the present study, transgenerational effects were evident since a lowered body weight and body fat and increased plasma glucose and insulin concentrations in the adult females of the UNAD high-fat-fed group compared with the control ADAD high-fat-fed group. Inadequate maternal nutrition has long-lasting detrimental effects on the health or phenotype of offspring. Epidemiological evidence from a period of severe famine (Dutch Hunger Winter) identified a clear relationship between maternal undernutrition during gestation and an increased risk of chronic diseases such as type II diabetes mellitus later in adult life of the offspring (16, 21, 32–34). Experimental models of developmental programming through undernourishment during pregnancy support these findings, with offspring demonstrating altered development and phenotypes. These offspring are often hyperphagic and have an
altered glucose, insulin, and leptin metabolism that manifests in increased blood pressure and obesity (14, 41). What is perhaps more important is that the effects of maternal undernutrition are identified in subsequent generations (trans-generation), as observed both in experimental models, such as this one, and from epidemiological evidence (9, 24, 37, 40).

The notable difference between previous studies and the current study is that UNAD females fed a high-fat diet had elevated rather than reduced plasma glucose and insulin concentrations compared with ADAD control females. Myostatin depletion leads to a reduction in the hyperglycemic state and adipogenesis in models of diabetes and obesity, whereas knockout and transgenic mice overexpressing the myostatin propeptide (an inhibitor of myostatin) and fed a high-fat diet show a resistance to both body weight gain and the development of insulin intolerance. These animals instead maintain a body weight equivalent to their chow-fed counterparts (28).

FSTL3-knockout mice also have increased insulin sensitivity, reduced visceral body fat, and increased pancreatic β-cell mass, resulting in a slight hyperinsulinemic state and altered fat and glucose homeostasis, due to the promoted uptake of glucose into fat and muscle (30). Therefore, it is important to recognize differences identified when myostatin and FSTL3-knockout models are used (15), as well as the administration of myostatin to obese animals (11), from those more complex differences evident across generations. It is also possible that members of the myostatin pathway have a role in systemic metabolic processes since the expression of myostatin receptor ActRIIB and inhibitor (FSTL3) are highly expressed in the adipose tissue of obese mice (1).

Given the ability for myostatin to function in numerous tissues, including placental and adipose tissue, as well as being a negative regulator of muscle growth supports speculation that myostatin may have a role in conveying the effects of abnormal gestational nutrition through to the offspring. In the current study, differences in placental and fetal weights between the groups were recorded at E20. Of particular interest was that the UNAD placentae were lighter than the ADAD placentae; however, no differences in fetal weight were observed between these groups. The placenta-to-fetus weight ratio of the UNAD group was observed to be similar to that of the ADUN group, and both were lower than that of the ADAD group. Therefore, it appears that the UNAD placentae, although lighter in weight, were supporting fetal weights equivalent to those of the ADAD fetuses.

Research into experimental reductions of placental growth resulting in changes to placental efficiency shows smaller placentae to be more efficient in transferring nutrients (10, 13). Therefore, morphological and functional changes found within these placentae (10, 13) may facilitate improved nutrient transport across the placenta, specifically glucose, the main nutrient needed across the placenta for the maintenance of fetal growth (18). Myostatin, through its ability to function in glucose homeostasis, may therefore have a role in increasing the efficiency of the placenta. In the present study, trans-generational undernutrition increased the placental expression of both myostatin and FSTL3 relative to adequately nourished controls. Increased myostatin mRNA expression was particularly notable, since myostatin actions occur predominantly through protein posttranslational modifications (20, 35). However, a change in myostatin and FSTL3 was not evident in
females undernourished within only one generation (ADUN group). Therefore, the increased expression of myostatin and FSTL3 in the UNAD group placental tissues could reflect an adaptive response in the second generation. However, further research is required to determine this and would be aided by the use of myostatin mutation, transgenic, or knockout mice models that have previously helped characterize the influence myostatin has upon phenotype, specifically body composition and metabolic sequelae, in relation to diet-induced and genetic obesity (15, 28, 45).

Myostatin is well known as a master regulator of early postnatal muscle growth, but dysregulation of myostatin can also lead to a reduction in adult muscle mass through negative regulation of the Akt/rapamycin (mTOR) signaling pathway (2). The E20 skeletal muscle tissue expression of myostatin was markedly lower in the UNAD compared with both ADUN and ADAD tissues. In contrast, the placental tissues at E20 showed an inverse pattern of expression. Therefore, the increased expression of myostatin in the UNAD placenta may alter or regulate the expression observed in offspring skeletal muscle tissues. However, in the mature skeletal muscle tissues both the effect of transgenerational undernutrition and the postnatal diet were identified, and both factors were linked to aberrant plasma metabolite concentrations in accord with a programming effect. Alternatively, the two systems, placental and skeletal muscle, may function independently since in the placenta the myostatin pathway (myostatin and FSTL3) was upregulated. The expression of myostatin was thus inversely related to FSTL3 in the UNAD high-fat-fed group, suggesting an inhibitory action of FSTL3 on myostatin in muscle related to maturity.

Our data also highlight that gestational undernutrition in the F1 generation, represented by the ADUN group, has no effect within one generation on the concentration of myostatin signaling pathway members in the placenta and skeletal muscle as well as the body composition or metabolic sequelae. Rather, it was only in the UNAD group that differences are evident. In the UNAD group, in which placental myostatin was altered, the resulting high-fat-fed offspring demonstrated elevated plasma glucose and insulin concentrations. Increased myostatin pathway signaling in the placenta that may modulate placental size and efficiency would thus allow exposure of the fetus to aberrant glucose concentrations in utero and “program” offspring to have increased susceptibility later in life when exposed to a high-fat diet, thus potentially providing an explanation for the disparity observed in previous studies.

Taken together, these studies provide strong evidence for advocating the importance of myostatin and its pathway members in the regulation of energy metabolism and the metabolic state in the fetus. The phenotype observed in the adult female offspring is potentially due to the combined effects of aberrant maternal nutrition and the effects conveyed by an altered placental expression of myostatin and FSTL3.

Thus, in summary, our data show that placental expression of myostatin and FSTL3 was influenced by transgenerational maternal undernutrition during gestation. These results indicate that placental myostatin may play a role in regulating nutrient supply and thus facilitate developmental programming over generations. Higher placental myostatin may also provide resistance to diet-induced obesity, albeit at the cost of glucose homeostasis. Further research into myostatin and its regulatory and signaling proteins within placenta will provide a better understanding for the role of myostatin in developmental programming and may provide a possible therapeutic mechanism against the aberrant changes seen due to transgenerational undernutrition.

ACKNOWLEDGMENTS

We thank Alice Coveny and Lara Kimble for their technical assistance with the animal studies and Janene Biggs for assistance with the DEXA analysis.

GRANTS

This research was supported by grants from the Maurice and Phyllis Paykel Trust, New Zealand, and The National Research Centre for Growth and Development, New Zealand, awarded to M. P. Green, and The Faculty Research Development Fund, University of Auckland, New Zealand, awarded to A. P. Ponnampalam.

DISCLOSURES

The authors of this manuscript have no conflicts of interest to declare.

REFERENCES


AJP-Endocrinol Metab • VOL 298 • APRIL 2010 • www.ajpendo.org


