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Maternal nutritional programming in the sheep: Effects on post-natal growth, mammogenesis and lactation in adult-ewe offspring

A thesis submitted for the degree of:

Doctor of Philosophy

In

Animal Science

at Massey University, Palmerston North, Aotearoa-New Zealand



MASSEY UNIVERSITY

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2014



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Abstract

Developmental programming is the concept that environmental factors, particularly during foetal life, can alter development, metabolism and physiology of an organism and this can have consequences later in life. There is growing interest in developmental programming in livestock species, particularly effects of maternal pregnancy nutrition, which is easy to manipulate. Recent research, using a sheep model, has shown that milk production in ewe offspring may be susceptible to maternal nutritional programming, such that over nutrition (*ad libitum*) of the pregnant dam, compared with maintenance nutrition, may impair their first lactation performance and result in the weaning of lighter lambs. The present study however revealed that maternal nutritional programming effects on lactation performance in ewe offspring did not persist over their productive lifetime.

In a new study, the critical programming period was narrowed down to early gestation, coinciding with early mammogenesis in the foetus. In this study only twin-born ewes were examined due to their economic significance in commercial sheep production and due to their increased susceptibility to nutritional insult *in-utero*. It was revealed that, in addition to over nutrition (*ad libitum*), under-nutrition (sub-maintenance) of the dam during early pregnancy also impaired first lactation performance of twin-born ewe offspring when compared with maintenance.

Transcriptomics analysis using RNA-seq identified that nutritional programming affects late pregnancy mammogenesis, rather than secretory cell function during lactation, in ewe offspring during their first parity. Ewes born to *ad libitum*-fed dams, in particular, appeared to have impaired regulation of cell cycle while ewes born to sub-maintenance-fed dams had reduced expression of genes associated with the extracellular matrix, both of which may influence cell proliferation. As a consequence, both ewes born to *ad libitum* and sub-maintenance-fed dams may have had fewer mammary secretory cells, resulting in reduced lactation performance.

The findings of this thesis indicate that differences in first-lactation performance of ewe offspring, as a result of maternal nutritional programming, may be mediated by impaired proliferation of secretory epithelial cells. These findings contribute to our knowledge of the mechanisms of developmental programming of the mammary gland and presents a platform for future investigations which may ultimately lead to the ability to manage and manipulate lactation performance.

Acknowledgements

I would like to acknowledge my Primary supervisor Professor Paul Kenyon and co-supervisors Dr Sarah Pain, Dr Sam Peterson and Professor Hugh Blair for their guidance and support throughout the journey of my PhD. I would also like to acknowledge the International Sheep Research Centre team for all their help along the way: Associate Professor Nicolas Lopez-villalobos for guidance with statistical analyses; Dean Burnham, Geoff Purchass and Natalia Martin for assistance with farm trials and for looking after my 'girls' (sheep); Dr Anne Ridler for assistance with biopsy procedures; and my fellow grad-students and friends: Maria Loureiro, Asmad Kari, April Adilletta, Lydia Cave, Erin Garnett, Gaby Gronqvist and Lisanne Fermin – for always being there to lend a hand and always bringing a smile to my face!

I would also like to thank Associate Professor Peter Dearden, Dr Liz Duncan (and everyone else) in the Lab for Evolution and Development, Genetics Otago, University of Otago, for hosting me, training me in molecular biology techniques, and for all of their immense help and support with the transcriptomics and gene expression studies... and for converting me to 'the dark side' - to molecular biology.

I must also extend gratitude to Gravida: Centre for Growth and Development for providing funding for research activities, training, and associated travel, in addition to a generous PhD stipend.

Last but not least I would like to thank my family, in particular my mum for always believing in me, and for her unwavering support and encouragement – you have truly been my rock through all of this!

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List of abbreviations

Ad = *ad libitum*
AdAd = *ad libitum* dam nutrition during early and mid-to-late pregnancy
AdHv = *ad libitum*-fed, heavy dam
AdLt = *ad libitum*-fed, light dam
AdM = *ad libitum* dam nutrition during early pregnancy and maintenance dam nutrition during mid-to-late pregnancy
ADP = adenosine diphosphate
Ad_{P21-50} = *ad libitum* dam nutrition during early pregnancy
Ad_{P50-140} = *ad libitum* dam nutrition during mid-to-late pregnancy
AI = artificial insemination
ATP = adenosine triphosphate
BCS = body condition score
BF = back fat
BHB = beta hydroxybutyrate
BR = birth rank
cDNA = copy DNA
CoA = co-enzyme A
CP = crude protein
CPY = crude protein yield
Cq = quantitation cycle (in RT-qPCR)
CY = casein yield
dsDNA = double-stranded DNA
E = ewe
E = oestrogen
EEF = eukaryotic translation elongation factor
EIF = eukaryotic translation initiation factor
EMA = eye-muscle area
ER = oestrogen receptor
ER α = oestrogen receptor type alpha
ER β = oestrogen receptor type beta
ETC = electron transport chain
FAS = fatty acid synthase
FEC = faecal egg count
FGF = fibroblast growth factor
FL = fore-leg
FY = fat yield
G0 = generation zero (dams fed differentially during pregnancy)
G1 = generation one (offspring born to G0 dams)
G2 = generation two (lambs born to G1 ewes, grand-offspring of G0 grand-dams)
gDNA = genomic DNA
GH = growth hormone
GHR = growth hormone receptor
GnRH = gonadotropin releasing hormone
HGF = hepatocyte growth factor

HL = hind-leg
HPA axis = hypothalamic-pituitary-adrenal axis
HTS = high-throughput sequencing
Hv = heavy
IDH = isocitrate dehydrogenase
IGF1 = insulin-like growth factor 1
IGF1-R = insulin-like growth factor 1 receptor
IGF2 = insulin-like growth factor 2
IGFBP3 = insulin-like growth factor binding protein 3
IGFBP6 = insulin-like growth factor binding protein 6
IHC = immune-histochemistry
ISH = in situ hybridization
JAK = Janus kinase
KGF = keratinocyte growth factor
L = lactation
LP = late pregnancy
LR = leptin receptor
Lt = light
LW = live weight
LWG = live weight gain (growth rate)
LY = lactose yield
M = maintenance
MAd = maintenance dam nutrition during early pregnancy and *ad libitum* dam nutrition during mid-to-late pregnancy
MAPK = mitogen-activated protein kinase
MD = muscle depth
MEC = mammary epithelial cells
MHv = maintenance-fed, heavy dam
MLt = maintenance-fed, light dam
MM = maintenance dam nutrition during early and mid-to-late pregnancy
M_{P21-50} = maintenance dam nutrition during early pregnancy
M_{P50-140} = maintenance dam nutrition during mid-to-late pregnancy
mRNA = messenger RNA
mTOR = mammalian target of rapomycin
NADH = nicotinamide adenine dinucleotide
NADPH = nicotinamide adenine dinucleotide phosphate
ncRNA = non-coding RNA
NE = net energy
NEY = net energy yield
P = day of pregnancy, e.g., P0 = day zero of pregnancy.
P = progesterone
P21-50 = day 21 to 50 of pregnancy (early pregnancy)
P50-140 = day 50 to 140 of pregnancy (mid-to-late pregnancy)
p53 = putative tumour protein 53
PCR = polymerase chain reaction
PL = placental lactogen

PPAR = peroxisome proliferator-activated receptors
PPP = pentose phosphate pathway
PR = progesterone receptor
Prl = prolactin
PrIR = prolactin receptor
R = ram
RER = rough endoplasmic reticulum
rRNA = ribosomal RNA
RT-PCR = reverse transcriptase PCR
RT-qPCR = quantitative (or real-time) RT-PCR
S = single (lamb)
SER – smooth endoplasmic reticulum
SmAd = sub-maintenance dam nutrition during early pregnancy and *ad libitum* dam nutrition during mid-to-late pregnancy
SmM = sub-maintenance dam nutrition during early pregnancy and maintenance dam nutrition during mid-to-late pregnancy
Sm_{P21-50} = sub-maintenance dam nutrition during early pregnancy
SREBP = sterol regulatory element binding protein
STAT = signal transducing activator of transcription
T = twin (lamb)
TAG = triacyl glycerol
TCA = citric acid cycle
TEB = terminal end buds
TGF = transforming growth factor
TGFβ = transforming growth factor beta
TP = true protein
TPY = true protein yield
TS = twin born, single reared (lamb)
VFA = volatile fatty acid
VLDL = very low density lipoprotein