REGULATION OF SOCS-3 EXPRESSION IN FETAL SHEEP TISSUES

Sheridan Gentili B.Sc. (Hons)

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School of Molecular and Biomedical Science

The University of Adelaide

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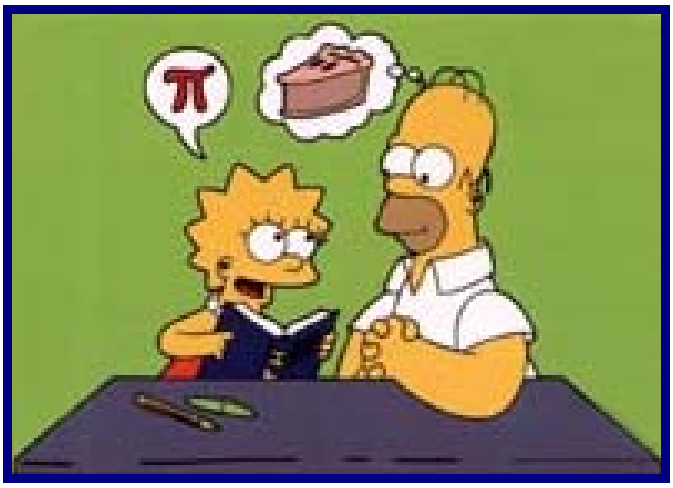

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ABSTRACT

The suppressor of cytokine signaling (SOCS) proteins have been identified as important regulators of cytokine signaling. SOCS-3 has been identified as being essential for normal fetal growth and survival, with the null mutation of the *socs-3* gene resulting in embryo death. The specific role of SOCS-3 in fetal development, however, has yet to be characterized. Therefore, the overall aim of this thesis was to identify and quantify SOCS-3 mRNA in a range of fetal tissues in the sheep. After identification of SOCS-3 expression in fetal tissues, we then aimed to determine the ontogenic profile of SOCS-3 in three key fetal tissues; the liver, adipose tissue and adrenal gland, and whether SOCS-3 expression in these tissues was altered after withdrawal and stimulation of prolactin (PRL).

SOCS-3 mRNA was found to be differentially expressed in a range of fetal tissues in late gestation and was higher in the fetal liver than in the pancreas, spleen and kidney. SOCS-3 expression increased throughout gestation in the fetal liver, however, its expression decreased in the fetal adipose tissue and adrenal in late gestation.

The pituitary hormone PRL has previously been implicated as a fetal growth factor. In the sheep fetus, PRL receptors are expressed in the fetal liver, adipose tissue and adrenal. We aimed to determine whether PRL plays a role in the maintenance of SOCS-3 expression in the liver, adipose tissue and adrenal gland in late gestation, and whether SOCS-3 expression can be regulated by acute PRL stimulation

We have demonstrated that PRL withdrawal suppressed SOCS-3 expression in the liver, whereas acute PRL stimulation upregulated SOCS-3 expression in the adrenal. Neither PRL withdrawal nor stimulation had an effect on SOCS-3 expression in the adipose tissue.

In summary, the data presented in this thesis would suggest that SOCS-3 has tissue specific functions in late gestation. Furthermore, its expression is regulated in a tissue specific manner in response to the withdrawal or acute stimulation by PRL This provides the first evidence to suggest that the fetal liver and adrenal are both sensitive to either chronic or acute changes in plasma PRL concentrations, measured as the suppression or upregulation of SOCS-3. We speculate that changes in SOCS-3 mRNA expression relates to the regulation of growth and functional maturation of fetal tissues throughout gestation, and that PRL may represent an important factor which acts to alter SOCS-3 expression in key fetal tissues.

DECLARATION

This work contains no material which has been accepted for the award of any other degree of diploma in any other university or tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except myself and where due reference is made in the text.

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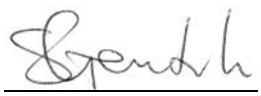

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PUBLICATIONS ARISING FROM THIS THESIS

GENTILI S, WATERS MJ AND MCMILLEN IC. Differential Regulation of Suppressor of Cytokine Signaling-3 (SOCS-3) in the Liver and Adipose Tissue of the Sheep Fetus in Late Gestation. *American Journal of Physiology – Regulatory, Integrative and Comparative Physiology* **290**, R1044-R1051

In preparation:

GENTILI S, SCHWARTZ JS, WATERS MJ, MCMILLEN IC. Prolactin and the expression of suppressor of cytokine signaling-3 (SOCS-3) in the sheep adrenal before birth.

Related publications, in preparation:

HYATT M, GOPALAKRISHNAN GS, BISPHAM J, **GENTILI S**, MCMILLEN IC, RHIND SM, RAE MT, KYLE CE, BROOKS AN, JONES C, BUDGE H, WALKER D, STEPHENSON T & SYMONDS ME. Maternal Nutrient Restriction in Early Pregnancy Programmes Hepatic Expression of GHR, PRLR, IGF-LIR, HGF, Bax and SOCS-3.

COMMONLY USED ABBREVIATIONS

A B C

ACTH	Adrenocorticotropic hormone
bp	Base pair(s)
Bromo	Bromocriptine
11βHSD	11 beta-hydroxysteroid dehydrogenase
cAMP	Cyclic adenosine monophosphate
cDNA	Complementary deoxyribonucleic acid
CIS	Cytokine inducible SH2 binding protein
CYP 11A1	Cytochrome P450 cholesterol-side chain cleavage
CYP 17	Cytochrome P450 17 α hydroxylase

D E F

D_2R	Dopamine type 2 receptor
d	Day(s)
Da	Dalton(s)
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetraacetic acid
EPO	Erythropoietin

G H I

GH	Growth hormone
GHR	Growth hormone receptor
h	Hour(s)
HPA-axis	Hypothalamo-pituitary-adrenal axis
HPD	Hypothalamo-pituitary disconnection
IFN-γ	Interferon-gamma
IGF	Insulin like growth factor
IL	Interleukin
IRS	Insulin receptor substrate

J K L

JAK	Janus kinase
JNK	Jun N-terminal kinase
Kb	Kilo base(s)
kDa	Kilo Dalton(s)
LIF	Leukemia inhibitory factor
l-PRLR	Long prolactin receptor
LPS	Lipopolysaccharides

M N O

MAPK	Mitogen activated protein kinase
min	Minute(s)
mRNA	Messenger ribonucleic acid
oPRL	Ovine prolactin

P Q R

PL	Placental lactogen
PO_2	Arterial partial pressure of oxygen
PHDA	Periventricular-hypophysial dopaminergic neurons
PR	Placental restriction
PRL	Prolactin
PRLR	Prolactin receptor
PKC	Protein kinase C
RT-PCR	Reverse transcription-polymerase chain reaction

S T U

Sal	Saline
SH2	Src homology 2 domain
SH3	Src homology 3 domain
SOCS	Suppressor of cytokine signaling
s-PRLR	Short prolactin receptor
STAT	Signal transducer and activator of transcription factor
TGF-β	Transforming growth factor–beta

THDA	Tuberohypophysial dopaminergic neurons
TIDA	Tuberoinfundibular dopaminergic neurons
TNF	Transforming nerve factor
UCP-1	Uncoupling protein -1

V W X Y Z

Y	Tyrosine

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