CYTOKINES AND LIPIDS IN PREGNANCY
EFFECTS ON DEVELOPMENTAL PROGRAMMING AND PLACENTAL NUTRIENT TRANSPORT

Akademisk avhandling

som för avläggande av medicine doktorexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 11 juni 2010, kl. 9:00

Av

Susanne Lager
Fil. Mag.

Fakultetsopponent: Docent Lucia Mincheva-Nilsson
Institutionen för klinisk mikrobiologi
Enheten för klinisk immunologi
Umeå Universitet
Umeå, Sverige

Avhandlingen baseras på följande delarbeten:

I. **Perinatal Lack of Maternal Interleukin-6 Promotes Development of Adiposity in Adult Mice**
S. Lager, I. Wernstedt Asterholm, E. Schéle, N. Jansson, S. Nilsson, J.-O. Jansson, M. Lönn, and A. Holmäng
Submitted

II. **The Effect of Maternal Triglycerides and Free Fatty Acids on Placental LPL in Cultured Primary Trophoblast Cells and in a Case of Maternal LPL Deficiency**
A.L. Magnusson-Olsson & S. Lager, B. Jacobsson, T. Jansson, and T.L. Powell
Am J Physiol Endocrinol Metab, 2007

III. **Effect of Cytokines on Fatty Acid Uptake in Cultured Human Primary Trophoblast Cells**
S. Lager, N. Jansson, A.L. Olsson, M. Wennergren, T. Jansson, and T.L. Powell
Submitted

IV. **Oleic Acid Stimulates System A Amino Acid Transport in Primary Human Trophoblast Cells Mediated by Activation of Toll-Like Receptor 4**
S. Lager, H.N. Jones, M. Wennergren, T. Jansson, and T.L. Powell
Submitted

UNIVERSITY OF GOTHENBURG

CYTOKINES AND LIPIDS IN PREGNANCY
EFFECTS ON DEVELOPMENTAL PROGRAMMING AND PLACENTAL NUTRIENT TRANSPORT

Susanne Lager

Section of Endocrinology, Department of Physiology, Institute of Neuroscience and Physiology,
The Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden

ABSTRACT

Metabolic disturbances, in particular those associated with nutritional challenges, that take place during development, both *in utero* and early postnatal life, have long-lasting health consequences on an individual. The most pronounced evidence of these challenges is a deviation in birth weight. This is a process recognized as developmental programming of adult health and disease. The etiologies of metabolic health disorders such as insulin resistance and obesity are complex; and developmental programming may be a factor contributing to the increased worldwide prevalence. Women who are overweight or diabetic have a higher risk for delivering large infants, and such infants are themselves at an increased risk of developing metabolic disturbances. Fetal growth is intimately linked to placental nutrient transport capacity. We hypothesized that the altered nutritional, hormonal, and metabolic environment of overweight or diabetic women (hyperlipidemia, pro-inflammatory status) modifies placental nutrient transport and contributes to altering the adult phenotype of these children. The aim of this thesis was to investigate the importance of maternal interleukin-6 during development for offspring adiposity and insulin sensitivity at an adult age in mice, examine the effects of cytokines and lipids on human placental nutrient transport functions and to describe mechanisms underlying these changes.

The main findings of this thesis were:
Interleukin-6 deficient mice weighed more and had a more pronounced adiposity which developed at a younger age if born of interleukin-6 deficient dams compared to dams with a heterozygote interleukin-6 genotype. At an older age (6 to 7 months of age) both groups had enlarged adipocytes and reduced insulin sensitivity. Wild-type mice fostered by interleukin-6 deficient dams also weighed more, had an augmented adiposity and larger adipocytes, and higher systemic leptin levels at an adult age compared to wild-type mice fostered by wild-type dams. Milk from interleukin-6 deficient dams contained twofold higher leptin concentrations compared to milk from wild-type dams. These observations suggest that lack of maternal interleukin-6 or, alternatively, factors modified by this cytokine have developmental programming effects that contribute to the development of adipose tissue and obesity.

Using primary cell cultures of human trophoblast cells, we demonstrated the production site of placental lipoprotein lipase to be cytotrophoblast cells and syncytiotrophoblast. We also observed that elevated levels of free fatty acids and triglycerides reduce trophoblast lipoprotein lipase activity; while insulin, interleukin-6, and tumor necrosis factor-α had no regulatory effect on lipoprotein lipase. Interleukin-6 did however increase placental lipid accumulation. Free fatty acids changed the release of cytokines from trophoblast cells and stimulated amino acid uptake through the System A transporter. Using RNA interference techniques, we demonstrated that toll-like receptor 4 is required for fatty acids to stimulate placental amino acid uptake.

In summary, we found that an altered maternal hormonal or metabolic environment can affect the developing fetus, causing long-term programming effects on adult phenotype. The effects of cytokines on placental lipid transport were moderate; however, there was a pronounced effect of fatty acids upon amino acid uptake. Therefore maternal circulating factors known to be altered in obesity may augment placental nutrient transport and contribute to an accelerated fetal growth.

Keywords: adipose tissue, amino acids, cytokines, developmental programming, free fatty acids, insulin resistance, interleukin-6, lipoprotein lipase, nutrient transport, placenta, toll-like receptor 4

ISBN 978-91-628-8087-3 Göteborg, 2010