The perinatal programming of metabolic diseases: Epigenetic resetting, the missing link?

Sylvain Sebert, H Budge & ME Symonds
A bit of redundancy...

Setting of energy balance

- Oxidation
- Storage

- Leptin synthesis
- Leptin sensitivity
- Ghrelin synthesis
Common factor – differential effects

Oxidation Storage

- Insulin resistance
- Insulin resistance
- CVD
- Type II diabetes
- CVD
- Obesity

Symonds, Sebert et al 2009
The perinatal period

Primordial functions & training

Fetal weight (kg)

Birth
The primary hypothesis...

Suboptimal maternal metabolic environment

Insulin  ->  Leptin
Cortisol  ->

Fetal adaptation for survival

Hales & Barker, 1992
Sheep as a model for obesity

Sheep - Humans

- Hyperinsulinemic
- Hypertension
- High free fatty acids
- Leptin resistant
- Hyper leptinemic

Sharkey, 2009 - Sebert, 2009 - Chan 2009
However…

Tygesen et al 2008

Glucose

BHB

FFA

Acetate

Fasting (ng/ml)

Insulin

Leptin

Cortisol

C

NR

Tygesen et al 2008
Alteration of energy available

Metabolomic PLS-DA on 139 VIP

Nutrient restricted

Control diet

Alexandre-Gouabau et al (poster) 2010
Remodelling of heart metabolism

mRNA (fold changes)

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* Chan, Sebert et al 2009
Cellular lipotoxicity

Glucose

FFA

GLUT1

FABP

Early programming of lipid metabolism?

ATP

Reactive Oxygen Species (ROS)
Remodelling of heart metabolism

Cardiac TG (mg/g)

mRNA (fold changes)

FTO Oxoglutarate-DNA demethylase

ATP

Energy

Chan, Sebert et al. 2009; Sebert, Chan 2010; Gerken et al. 2007
Influence on food intake

**mRNA (fold changes)**

- **MC4R**
- **AMPk**
- **FTO**

**Food intake (MJ/kg)**

- **C**
- **NR**

Sebert, Hyatt et al 2009 – Sebert, Chan et al 2009
Energy sensing

AMP

AMPK

ATP

Energy

mTOR

ATP

R.O.S

NFκB
IUGR, Remodelling & obesity

**Sharkey, Fainberg et al, 2008**
Unfolding protein response

DNA degradation
Apoptosis

GRP 78

CHOP
Endoplasmic Reticulum stress

The University of Nottingham
Early oxidative epigenetic settings

Mitochondrial function
- AMPK, mTOR, FTO

Mitochondrial biogenesis
- PGC1, SIRT1

DNA stability - remodelling
- CHOP, GRP 78
Other models of IUGR

Coupe et al, 2010
Maternal obesity

Maternal metabolism

Placental oxidative stress

↑DNMT1

![Diagram showing the relationship between maternal obesity and placental oxidative stress with increased DNMT1 expression and correlation with fetal weight.](image-url)
Setting of constitutive expression

Histone acetylation/methylation

DNA methylation

miRNA

RNA Stability

Splicing
Not an epiphenomenon...

Thompson et al 2010
New tools...
...with a better understanding

Metabolomic PLS-DA on 2000 VIP in adulthood

NR + rapid postnatal growth

Control

Alexandre-Gouabau et al (poster) 2010
Thank you!

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