Epigenetics of Leptin and Early Life Weight Trajectory

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Epigenetics of Leptin and Early Life Weight Trajectory

• What is leptin?
• Physiology of leptin
  – Adult
  – Pregnancy
  – Early life
• Epigenetics of leptin in early life
  – Maternal glucose
Leptin discovery: first adipokine

Zhang et al. Nature 1994
Leptin is an adipostat signal for weight regulation

Farooqi S et al. *NEJM* 1999; Farooqi S et al. *JCI* 2002
Hypothalamus integrates leptin adipostat signal

Normal physiology negative feedback loop

Obesity = leptin resistance

Heymsfield S. JAMA 1999
Leptin also acts in reproductive system

- Central actions
  - Hormone regulation
  - Food intake
  - Energy expenditure

- Vascular function
  - Atherosclerosis
  - Angiogenesis
  - Oxidative stress

- Reproduction
  - Placental function
  - Trophoblast invasion
  - Foetal function
  - Gonadotrophins and gonadal hormones

- White adipose tissue

- Bone and cartilage
  - Regulation of bone mass
  - Rheumatoid arthritis
  - Osteoarthritis
  - NO
  - Chondrocytes

- Immune system modulation
  - Cytokine induction
  - Chemotaxis
  - Macrophage activation
  - Natural killer cytotoxicity
  - $T_H^1$ stimulation
  - $T_H^2$ inhibition
  - Increase of maturation and survival of thymic T cells
  - Increase of IL-2
  - Naive T-cell proliferation
  - Dendritic cells activation

Leptin is produced by placenta

Placenta greatly contributes to maternal circulating levels

Hauguel-de Mouzon S, Am J Obst Gyn 2006
Maternal leptin

Fetal leptin

maternal fetal

adipose tissue

Placenta

adipose tissue

Maternal leptin

Fetal leptin

Launch Course
Gen3G: Prospective observational cohort population-based

Visit 1: recruitment
- Between 6-14 weeks of gestation
  - 2010-2013
  - N = 1024 women
- Consent forms
- Questionnaires
- Blood samples

Visit 2
- Between 24-28 weeks of gestation
  - N = 898
- Questionnaires
- 75g-OGTT

Visit 3
- At delivery
  - N = 854 with full data (OGTT)
- Anthropometry
- Cord blood samples
- Placenta samples

Maternal leptin

Fetal leptin

N = 712
Maternal leptin

Fetal leptin

Gestational weight gain

Lacroix M et al. *in prep*

Patenaude J et al. *in prep*
Leptin in critical perinatal period determines hypothalamic development

Bouret S et al. Science 2004
Leptin in critical perinatal period influences weight trajectory and adipocytes size.
Predictors of early infancy weight gain
Weight-for-length from birth to 6 months

M. Parker et al., J Pediatr. 2011
Low leptin in cord blood at birth is associated with higher weight status at 3 years old


Model adjusted for maternal education, prepregnancy BMI, gestational weight gain, duration of gestation, paternal BMI, child age, gender, race/ethnicity, and breastfeeding duration
Cord blood leptin predicts lower 3-y BMI, but age 3 leptin predicts higher 7-y BMI → early sensitive period of leptin action

Mantzoros et al. Pediatrics 2009
Boeke et al, Obesity 2013
Maternal leptin
Fetal leptin

Gestational weight gain

Age 3 Adiposity
Age 7 Adiposity

Hormone regulation
Food intake
Energy expenditure

Central actions
Epigenetics of Leptin and Early Life Weight Trajectory

- What is leptin?
- Physiology of leptin
  - Adult
  - Pregnancy
  - Early life
- Epigenetics of leptin in early life
  - Maternal glucose
Maternal hyperglycemia is associated with differential DNA methylation levels in placenta.

- Higher maternal glycemia
- Lower expression
- Higher methylation
- Lower expression

Bouchard L et al. *Diabetes Care* 2010
Mendelian Randomization helps to assess causality in observational studies.
Mendelian Randomization can be applied to assess causality in fetal leptin epigenetic programming supporting that maternal glycemia is part of the causal pathways influencing offspring leptin epigenetic regulation.

Fasting glucose 2\textsuperscript{nd} trimester $\rightarrow$ cg12083122 in Cord blood $\rightarrow$ Cord blood leptin (log)

$\beta = 0.56; \ SE = 0.12$
$P = 4.52\times 10^{-6}; \ N = 478$

Allard C et al. \textit{in revision}
Maternal leptin
Fetal leptin
Maternal glycemia
Other factors?

Gestational weight gain
Age 3 Adiposity
Age 3 leptin
Age 7 Adiposity

Maternal adipose tissue
Fetal adipose tissue
Placenta
Hormone regulation
Food intake
Energy expenditure
Central actions
Take home messages

• Perinatal period is critically sensitive to leptin
  – Likely affect many tissues
  – Associated with early life weight trajectory
• Maternal glucose modulates epigenetic regulation of leptin in offspring
Acknowledgements

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- Harvard School Public Health: A Baccarelli, A Litonjua, D Demeo
Questions
Mendelian Randomization can be applied to assess causality in maternal-fetal epigenetic programming

Relton C; *Int J Epidemiol* 2012
Maternal glucose influences epigenetic regulation of leptin in offspring

**Step 1**
- GRS for fasting glucose (10 SNPs)
  - $\beta_{G1} = 0.046$
  - $P = 7.8E-11$
- Fasting glucose 2nd trimester
  - $\beta_{IV1} = -0.072$
  - $P = 0.05$
- cg12083122 in Cord blood
  - $\beta_{OBS1} = -0.431$
  - $P = 0.07$
- Cord blood leptin (log)

**Step 2**
- $G_0$?
  - $\beta_{IV2}$
- Fasting glucose 2nd trimester
- cg12083122 in Cord blood
  - $\beta_{OBS2} = -0.170$
  - $P = 0.01$
- Cord blood leptin (log)

Allard C et al. *in revision*
Mendelian Randomization modeling LDL vs HDL for myocardial infarction

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*</th>
<th>Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL cholesterol</td>
<td>1.54 (1.45–1.63)</td>
<td>2.13 (1.69–2.69), p=2×10⁻¹⁰</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>0.62 (0.58–0.66)</td>
<td>0.93 (0.68–1.26), p=0.63</td>
</tr>
</tbody>
</table>

*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Table 4: Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

Voight B et al. Lancet 2012
Perinatal hormones (esp. leptin) → Early infancy weight gain → Obesity

- : Decrease
+ : Increase
Differential associations of leptin with adiposity across early childhood