Biological Determinants: Developmental Origins

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Biological Determinants: Developmental Origins

1. Overview of developmental programming and evidence for the importance of the developmental environment in determining offspring – particularly female offspring phenotype.

2. Mechanisms whereby a female offspring’s phenotype is changed by her developmental environment thus putting her own later pregnancy at risk.

3. Transgenerational effects.

Programming
The process through which a stimulus or insult establishes a persistent response.

Developmental programming hypothesis
Exposure during a critical period in development may influence phenotype - life time function and health.
Developmental Programming

The idea that our life-time health is as much impacted by the conditions under which we develop in the womb and early life as by our genes is a paradigm shift in our thinking of what needs to be done to improve the health of the nation. We need to think in terms of gene-environment interactions.
We pass more biological milestones before we are born and in the early months as a baby than at any other time in our lives.

How we pass these milestones will be greatly affected by our very first environments, the womb and immediately after birth.
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Blood cholesterol in men and women at the age of 50 can be related to the extent to which they had to protect their brain when they were fetuses.
How do we know that nutrition in pregnancy is important?
A young Pima woman
High Type 2 Diabetes

Low Type 2 Diabetes
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The couch potato rat.

Severe maternal undernutrition (30% normal diet) induces increased fat mass and reduces offspring locomotor activity.

*Vickers MH et al., 2000;2001; 2003*

Voluntary locomotor activity
Cardiovascular variables allometry and plasma analytes in six month old offspring of fat mice.
Immunohistochemistry in 0.9 G fetal baboon pancreas CTR (A-C) and MNR (D-F). IGF-1 (A,D); IGF-2 (B,E) and insulin (C,F).
Fetal pancreatic Insulin fraction and density from *ad lib* fed controls baboons (CTR, n=7) or nutrient restricted (MNR; fed 70% CTR; n=7) from 0.16 to 0.9G. Data M ± SEM. *p< 0.05.
Effects of maternal obesity on fetal development in the sheep.

The sheep is widely used as a biomedical model for human pregnancy, and is the only model large enough to study the challenged fetus directly combined with an evaluation of post-natal effects.
Methods

• Multiparous Western Whiteface ewes carrying singleton fetuses were fed a high energy diet at 100% (controls) or 150% (Obese) of NRC recommendations from 60 days before conception to day 75 of gestation.

• A subset of ewes were subjected to a GTT on day 75.

• A second set of ewes were necropsied on day 75 of gestation and the fetus recovered.

• A third set of ewes were allowed to deliver.
The first half of gestation is critical for:

1) Placental growth and vascularization

2) Fetal organogenesis: fetal organs shown to be most affected by early gestational under nutrition include the pancreas.
Vascularity in both CAR and COT tissues of OB and C ewes at d 75 of gestation.
Relative Content of FATP1, FATP4 and CD36 protein in COT of Control and OB Ewes on Day 75 of Gestation

C    C   OB   OB

FATP1
FATP4
CD36
Tubulin

Mean ± SEM; **: p<0.01; n=5 in each group.

control fed ewes;   obese over-nourished ewes:
Placental macrophages in obese women. A: placental sections from a lean (pre-gravid BMI: 22.5) woman - rare Macrophage staining; an obese (pre-gravid BMI: 31.7) woman with increased numbers of macrophages (C) and (D). Right: Placental macrophage number. $M \pm SE$. *: $p < 0.001$ obese vs lean. Lower panel: macrophages (thick arrows) in the villous stroma Thin arrow: syncytiotrophoblast nuclei,#: fetal blood space, *: maternal blood space. Scale 20 µm. J.C. Challier et al Placenta 29 274-281
Concentration of Glucose and Insulin in Maternal Blood on 0.5 Gestation in the obese sheep model.

Area Under the Curve differs by dietary treatment (P<0.05)
Glucose Content in Both Maternal and Fetal Blood on D75 of Gestation

*Means ± SEM differ (P<0.05)
Beta cells in the pancreas of the fetal sheep

Fetal beta-cells in obese mother

Fetal beta-cells in control mother
Insulin Content in Both Maternal and Fetal Blood on D75 of Gestation

*Means ± SEM differ (P<0.05)
Effect of obesogenic diet on fetal muscle histology

Con fetal muscle

OB fetal muscle
Cortisol in Control (CTR, n=6) maternal nutrient restricted (NR, n=6) and overfed (Fat, N=6) ewes and fetuses at 78 days of gestation.

* p< 0.05 compared to CTR group.
Post natal data

We have evaluated glucose handling at two months of age.
Concentration of Glucose and Insulin in Lambs at 2 Months of Age

Compared to Control group (C): *P<0.05; + p=0.07.
Risk of Overweight in Adolescence By Duration of Breastfeeding in Infancy

Gillman MW et al, JAMA 2001 285, 2461-2467
What are the possible mechanisms for the programming of a predisposition to obesity?
Effects of maternal dietary protein restriction and folic acid supplementation during pregnancy in rats on gene promoter methylation and RNA expression in the offspring 34 d after birth

Diets: C 18% protein, 1mg/kg folic acid (■); R – 9% protein, 1 mg/kg folic acid (□); RF – 9% protein, 5mg/kg folic acid (▲). Values are mean ± SD, n=10 offspring/maternal dietary group. *P* < 0.05: a) vs C; b) vs RF.

Lillycrop K et al.
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Windows of Development

At birth litters were adjusted to 12 pups/litter

Time line

Day 0 22 0 21 ~130 0 21 0 21 0 21
Gestation Lactation Growth

Control

Restricted

Control

Restricted

Control

Restricted

Control

Mothers

Pups

Puberty

Adult life

Cyclic

Restricted

Control

Restricted

Control

Control

Control
Programming of Obesity

22 month old female offspring from dams fed control (CC) and restricted (RC) diets

Transgenerational effects of maternal under nutrition on insulin resistance in granddaughters and grandsons.

Insulin Resistance Index (IRI) in granddaughters and grandsons of rats fed either control (C - 20%) protein or restricted (R – 10%) protein diet during pregnancy (first letter) or lactation (second letter); mean ± SEM; n=12 -16.
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