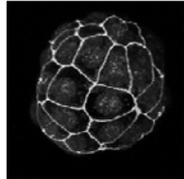
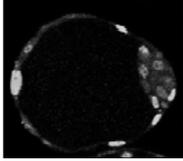


Maternal diet, embryo effects and offspring health

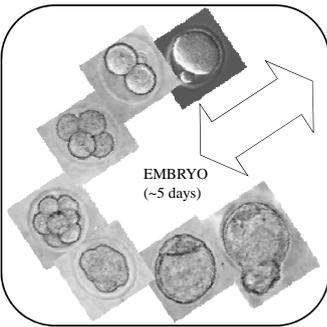


Tom Fleming
Univ Southampton, UK
ESHRE Workshop, Stresa, Italy April 2012
Mammalian Folliculogenesis and Oogenesis

The Responsibility of Motherhood *- it can be scary!*



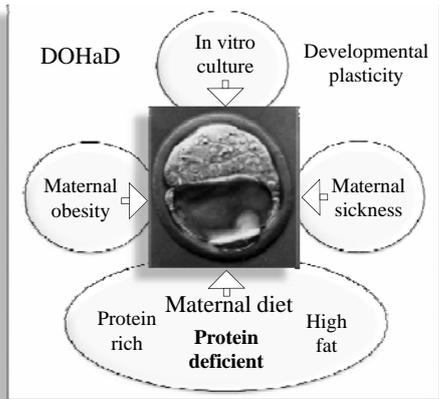
MOTHER



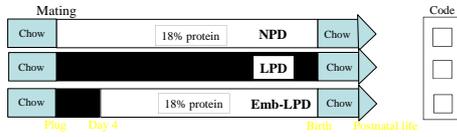
EMBRYO
(~5 days)

Maternal-embryonic communication:
Short-term:
• Fertilisation
• Blastocyst morphogenesis
• Coordination of implantation
• Maternal immunotolerance
Long-term:
• Developmental plasticity - 'selecting' the right phenotype to fit future environment
Implications: DOHaD; ART, IVC, maternal health at conception

Periconceptional Environment



Mouse Low Protein Diet Model



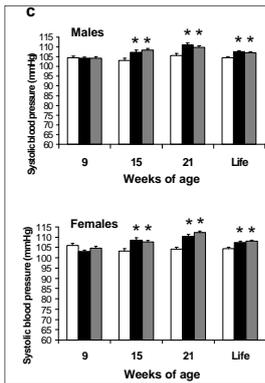
Diet Composition (g/kg)		
	18%	9%
Casein	180	90
Corn starch	425	485
Fibre	50	50
Sucrose	213	243
Choline chloride	2	2
DL-Methionine	5	5
AIN-76 mineral mix	20	20
AIN-76 vitamin mix	5	5
Corn oil (g/ml)	100	100

- Iso-caloric
- Derived from Langley & Jackson, 1994

- **Mild challenge:** 9% protein is sufficient for non-pregnant rodent – therefore not starvation but normal range
- **Large study:** (19 mothers, 114 offspring per treatment) allows detailed associations to be identified
- No effect on gestation length, litter size or male:female ratio

Watkins et al. (2008) Biol Reprod 78:299

Maternal Emb-LPD and Postnatal Cardiovascular Phenotype



Adult Emb-LPD offspring exhibit:

- Relative hypertension
- Smaller heart mass (females)
- Increased lung ACE activity
- Reduced arterial vasodilatation

Watkins et al. (2008) BOR 78:299
Watkins et al (2010) Br J Nutr 103:1762-70

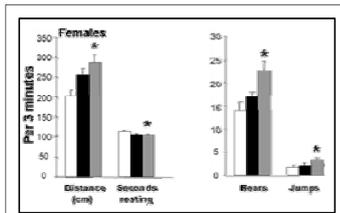
Similar datasets:

Rat Emb-LPD, Kwong et al, 2000, Development
Mouse LPD during oocyte maturation,
Watkins et al, 2008, J Physiol
Mouse ART culture, Watkins et al, 2007, PNAS

- LPD
- NPDP
- Embryo-LPD

Maternal Emb-LPD and postnatal behaviour

- Assays measure anxiety-related locomotor and exploratory activities
- Mean of tests repeated five times over weeks 8, 11, 14, 17 and 20 after acclimatization
- **Emb-LPD offspring exhibit 'hyperactive' behaviour**



- LPD
- NPDP
- Embryo-LPD

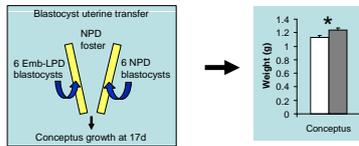
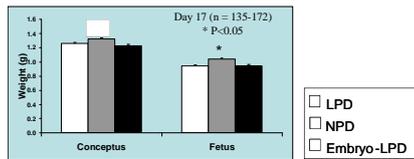
with Hugh Perry and colleagues

Watkins et al. (2008) BOR 78:299

CLINICAL RELEVANCE:

- **Systolic and diastolic blood pressure** levels higher in IVF children (8-18 years) than controls ($P < 0.001$) (Ceelen M et al (2008) *J Clin Endocrinol Metab.* 93:1682-8)
- **Growth velocity** higher in IVF children and is predictive of later elevated blood pressure (Ceelen et al, 2009) **Increased early growth** → **disease**
- **Birth weight** (+/- adjusted for gestational age, gender) of IVF children significantly different dependent upon commercial culture medium used (Dumoulin et al 2010 *Human Reproduction* 25:605-612)
- **Dutch winter famine**, 5 months, 1944-45, Amsterdam: Offspring from women exposed to famine during **embryo and early gestation** show
 - increased prevalence of coronary heart disease; increased blood pressure
 - increased BMI and glucose intolerance
 Painter et al, 2006a,b; de Rooij et al, 2006; Ravelli et al, 1999.

When do responses to maternal diet occur?



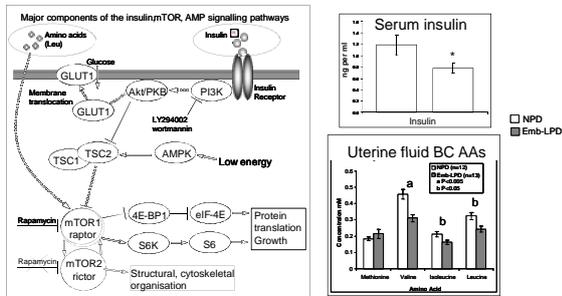
Increased perinatal growth in Emb-LPD conceptuses is detectable in late gestation, a response **induced by the blastocyst stage** independent of later maternal environment

Rose Pantou, Tom Papenbrock

Watkins et al. (2008) BOR 78:299

How do embryos sense their mother's nutritional status?

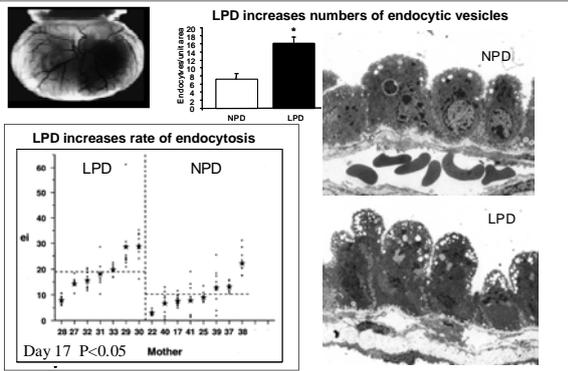
A role for amino acids, insulin and mTOR signalling



Depleted maternal insulin and branch chain AA availability following Emb-LPD

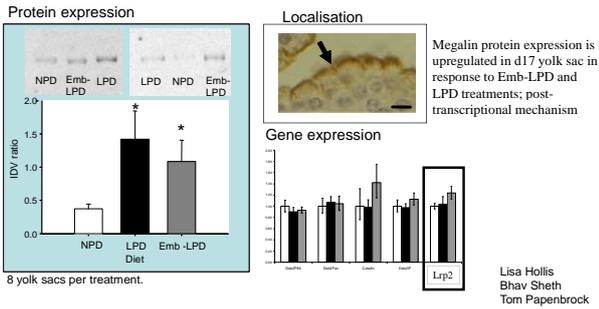
With Richard Porter, Henry Leese

Maternal LPD induces responses in the visceral yolk sac



Visceral yolk sac megalin (Lrp2 gene)

- 600 kDa transmembrane multi-ligand (~35) endocytic receptor, LDL-R family
- localised to apical surface of yolk sac visceral endoderm
- major role in yolk sac endocytosis



Response by trophectoderm to maternal Emb-LPD treatment: increased proliferation and cell spreading

