Programming of mammary development in ruminants

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What is programming?

Influences during early developmental stages, particularly during fetal life, leading to physiological and metabolic changes that have consequences later in life *Barker, 1997; Gluckman and Hanson 2004*

Key influencers include:

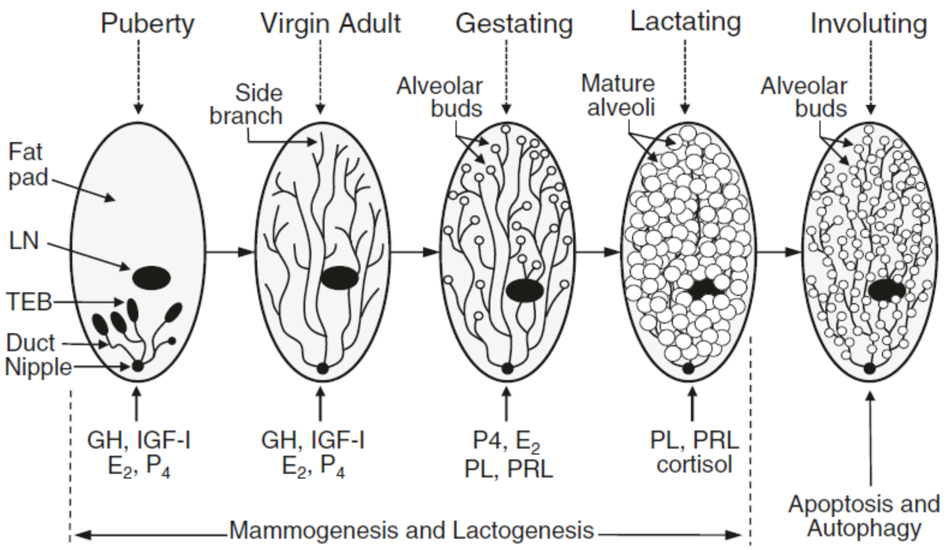
- Nutrition (amount, composition, specific nutrients)
- Fetal growth restriction (nutrition, dam size, dam age, environment, disease)

Target tissues/organs:

- Heart, kidney, liver, pancreas, adipose tissue, skeletal muscle, mammary gland

Mammary gland development

- Structural development of the mammary gland is critical for milk production
- 5 phases of mammary development:
  1. Fetal
  2. Pre-pubertal ?
  3. Post-pubertal
  4. Pregnancy
  5. Lactation



Source: Rezaei et al. 2016

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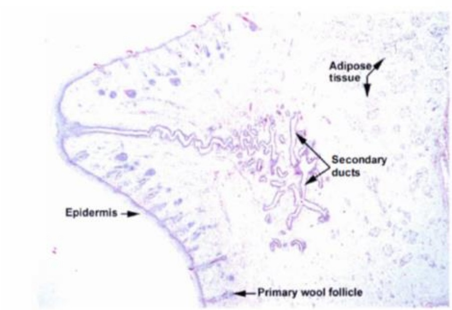
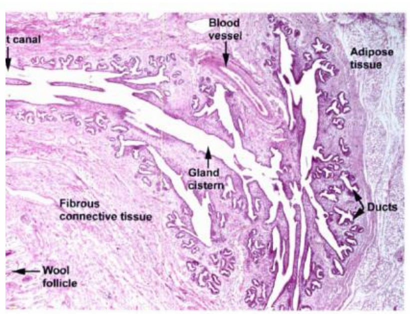
Early life mammary development

- Mammogenesis initiated in embryonic and fetal life - fat pad develops separate to epithelial component in ruminants *Hovey and Aimo 2010*
- Mammary growth ↑ rapidly in early postnatal life
- Developmental changes occur in the way the mammary gland responds to environmental stimuli *Geiger et al. 2016; Brown et al. 2005*
- Early life events influence future milk yield in sheep and dairy cattle *van der Linden et al., 2009; Paten et al. 2017; Soberon et al., 2012*

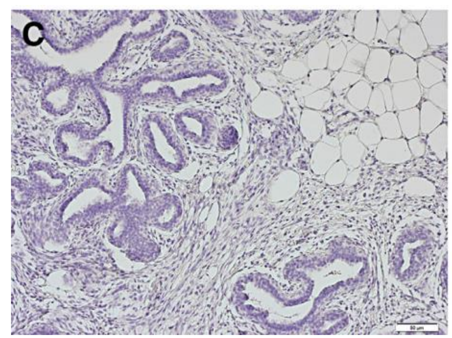


100 day gestation ovine fetus

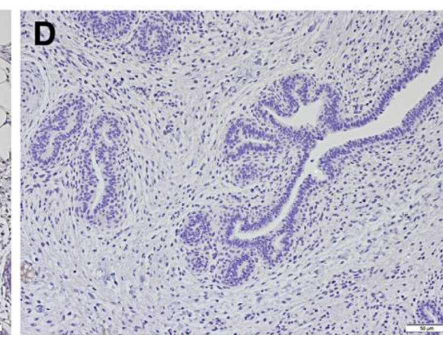


140 day gestation ovine fetus

Jenkinson 2003 – PhD thesis



Pre-pubertal lamb

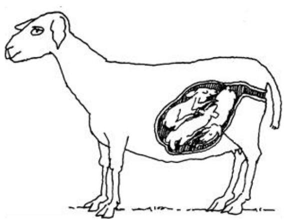


Pre-pubertal heifer

Source: Rowson et al. 2012

Fetal/neonatal programming of mammary development

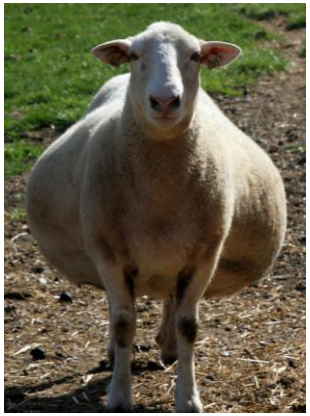
Future lactation performance?



Nutrition

Fetal/neonatal mammary gland development

Knowledge of biochemical changes and molecular pathways to identify mechanisms may inform intervention strategies



Fetal mammary development – ovine study

Neonatal mammary development – bovine studies

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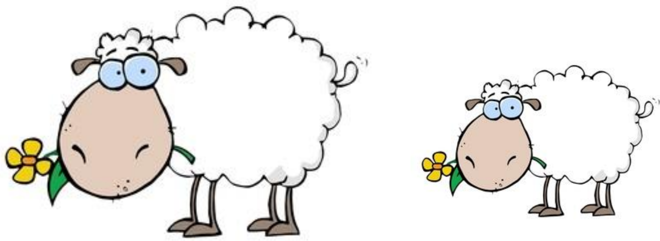
Influence of dam weight and plane of nutrition during gestation on fetal mammary development and future lactation performance

2 x 2 factorial



61 vs 43 kg

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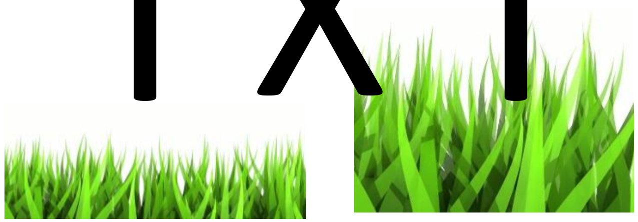


1300 vs 2300 kg DM/ha
d21-140 gestation

Kenyon et al., 2009; van der Linden et al. 2009

Dam size:

Progeny of large *vs.* small ewes had ↑ first lactation milk yield

- ↑ duct area at day 100 but no difference at day 140 of gestation

Dam nutrition:

Progeny of maintenance *vs. ad libitum* fed ewes had ↑ first lactation milk yield

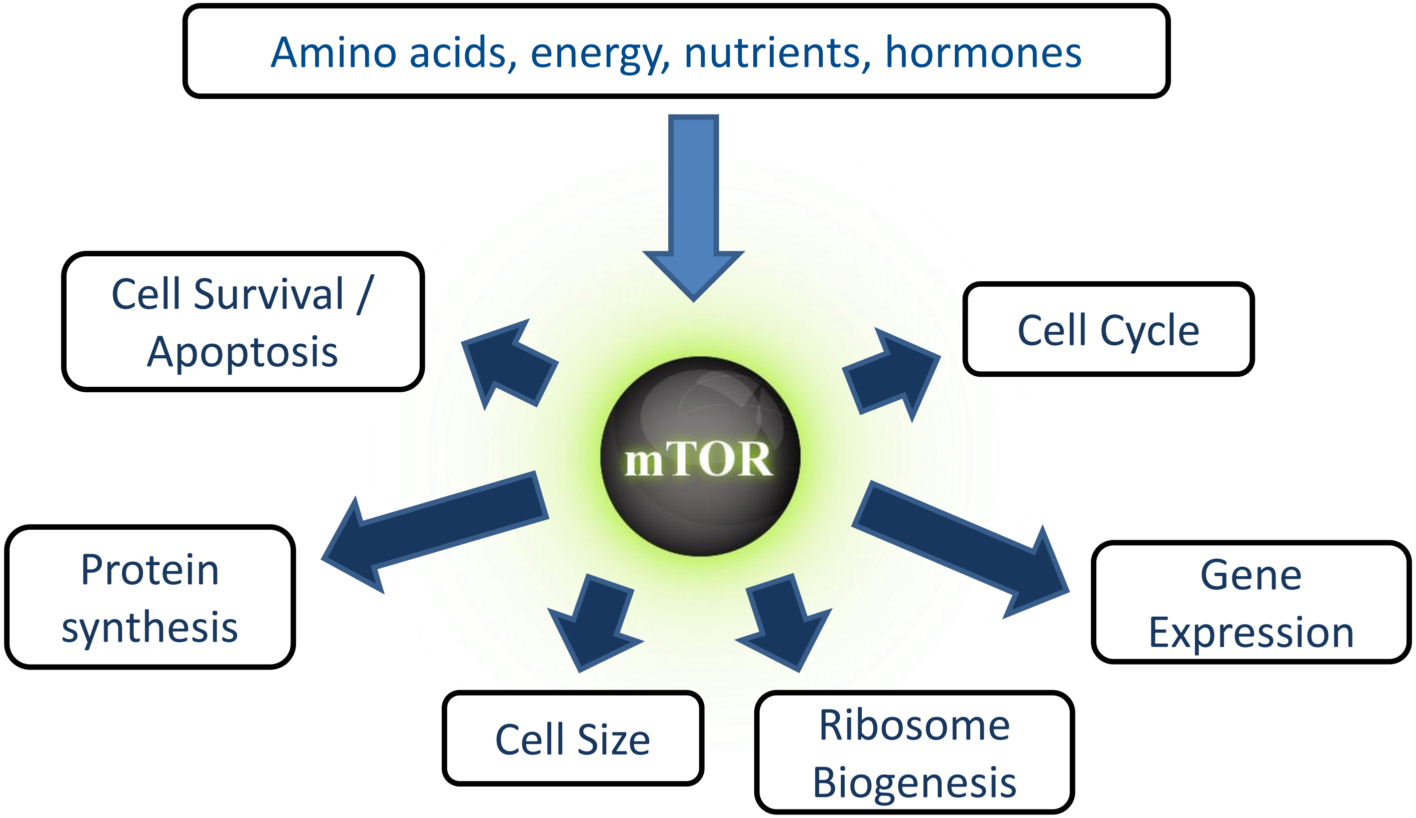
- No effect on mammary ductal development at day 100 or 140 of gestation

van der Linden et al 2009, Paten et al 2017, McCoard et al. 2018

Influence of dam nutrition on cellular development and signalling networks?

The mTOR Pathway

(mammalian target of rapamycin)

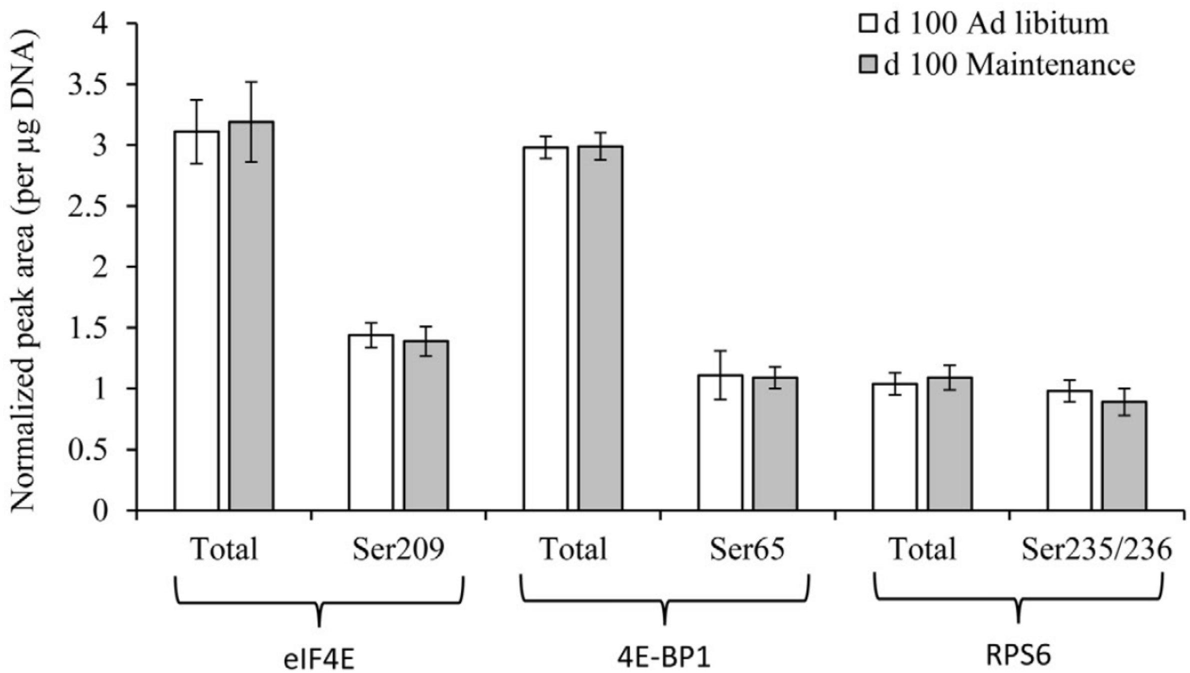


cellular “nutrient sensor”

Results

Day 100 gestation:

- Mammary weight: Maintenance 14% > *Ad lib* (P=0.03)
- No difference in biochemical indices
- No difference in mTOR/MAPK signalling



Sciascia et al. (2015) J. Anim. Sci. 93:699-708.

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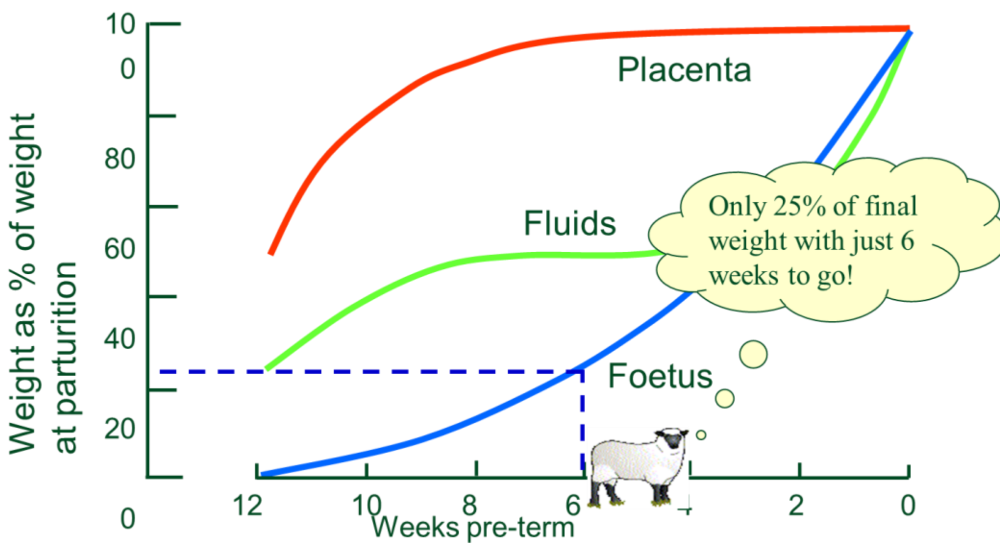
Day 140 gestation:

- Mammary weight: Maintenance 25% < *Ad Lib* (P=0.07) - Reverse of d100
- Hyperplasia or cell number (total DNA): Maintenance 44% < *Ad lib* (P=0.04)
- Hypertrophy (protein content/cell size): Maintenance 25% < *Ad lib* (P=0.09)

No change in parenchymal development but ↓ in mammary size implies ↓ fat pad mass



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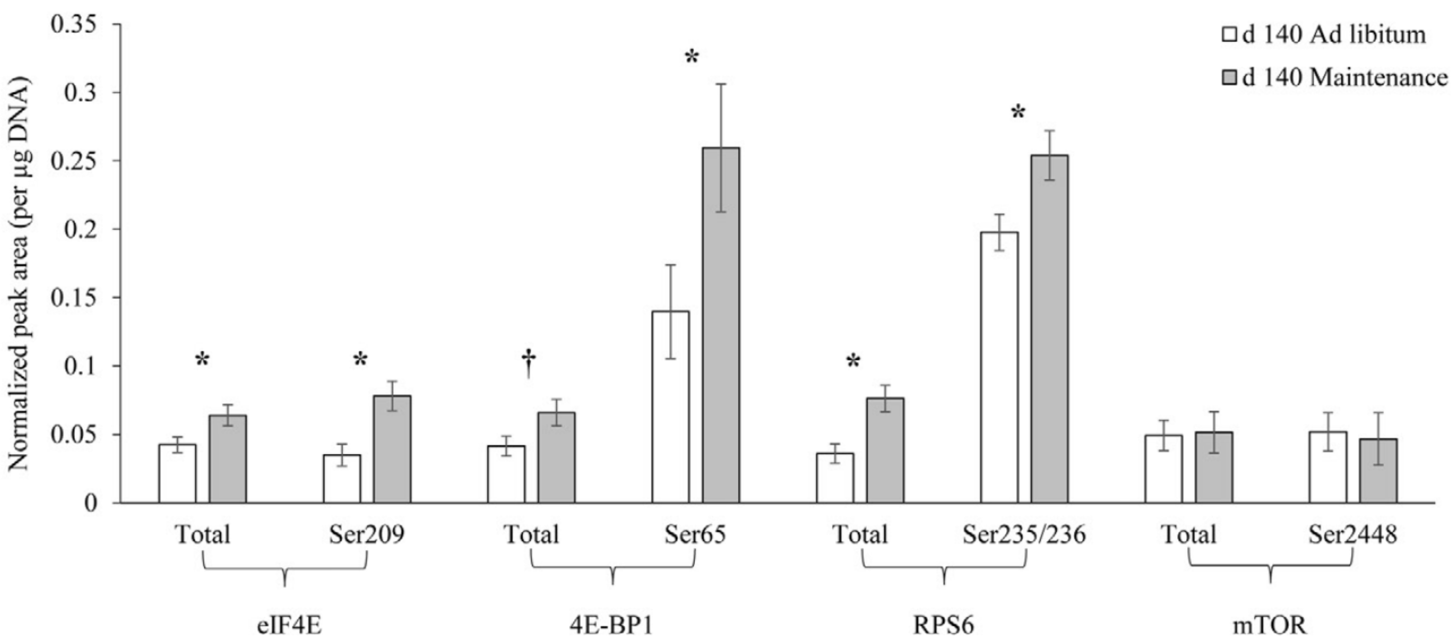
Day 140 gestation:

- Protein synthetic capacity (RNA:DNA ratio) 73% ↑ in Maintenance *vs Ad lib*
  - ↑ abundance of MAPK pathway proteins (eIF4E)
  - ↑ abundance of mTOR pathway proteins (4E-BP1)
  - ↑ ribosomal protein S6 abundance

↑ protein synthetic capacity via ribosome biogenesis and availability of factors required to initiate protein translation



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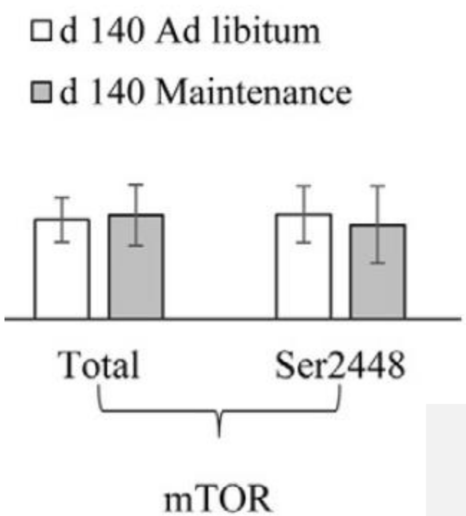
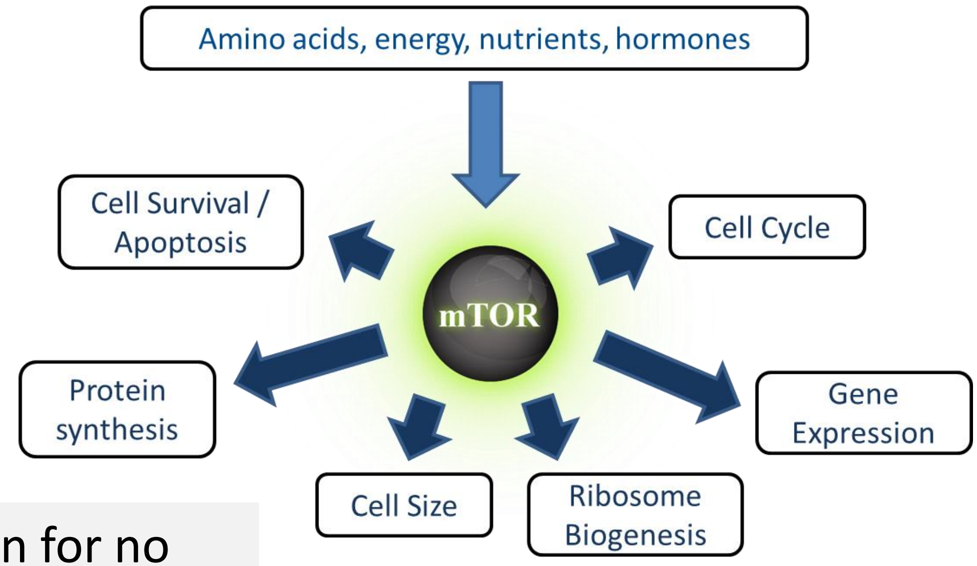
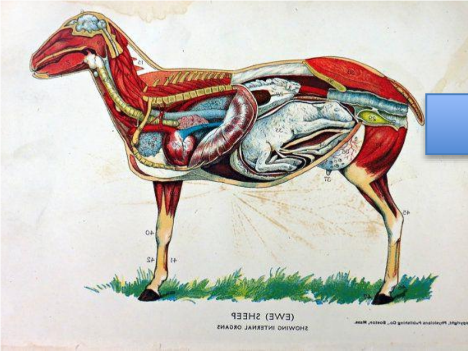


Explanation for no change in mTOR?



Evaluated abundance of each factor in fat pad and parenchyma from a separate study *McCoard et al., 2013*

- mTOR^{Ser2448} primarily found in the fat pad not parenchyma
- All other factors present in both fat pad and parenchyma
- May explain the lack of difference observed in combined fat pad + parenchyma sample



↓ Dam nutrient intake in gestation

↓ Fetal nutrition restricting growth

↓ Fetal mammary fat pad mass in late fetal life

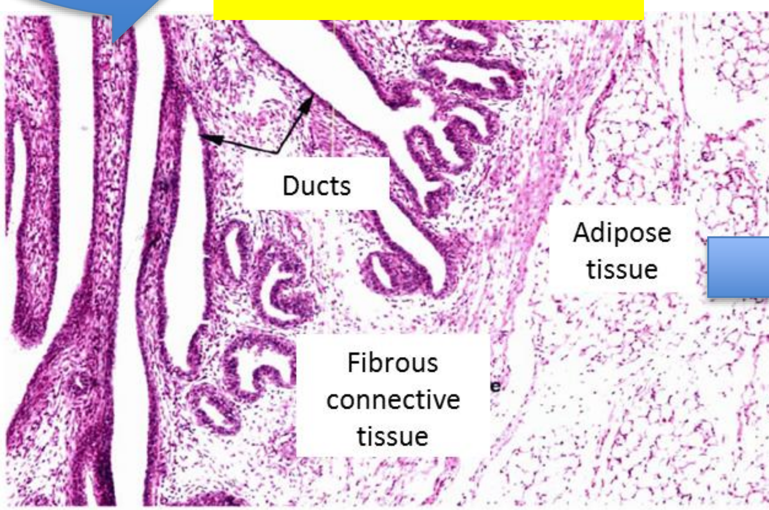
↑ 1st lactation milk yield

↑ Protein synthetic efficiency

↑ Ribosome biogenesis and factors required to initiate protein translation

↑ MAPK/mTOR signalling (fat pad)

“priming” mechanism?



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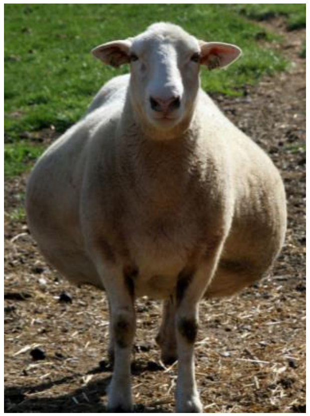

Fetal mammary development – ovine study

Neonatal mammary development – bovine studies

Pre-weaning and pre-pubertal growth affect future milk yield in dairy cattle

Soberon et al., 2012; Khan et al., 2011; Davis Rincker et al., 2011; Geisinger et al., 2016

Pre-weaning milk volume influences growth rate (~700 vs 500 g/d), mammary gland mass and fat cell size in calves at 6 weeks

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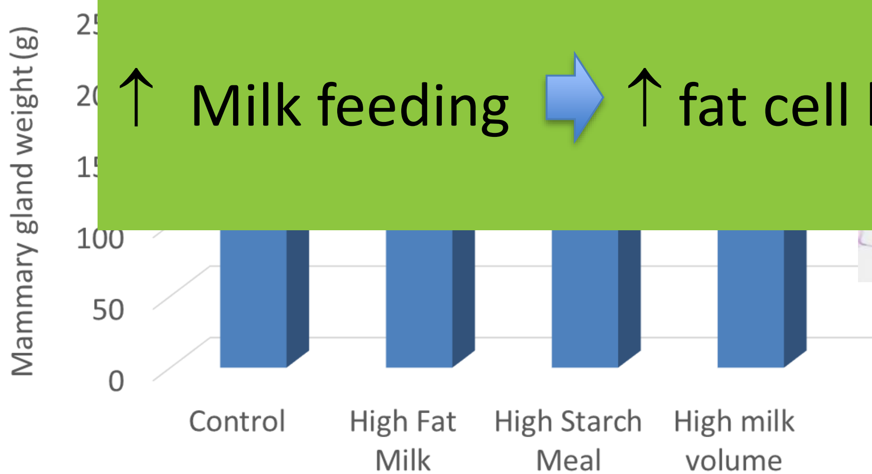
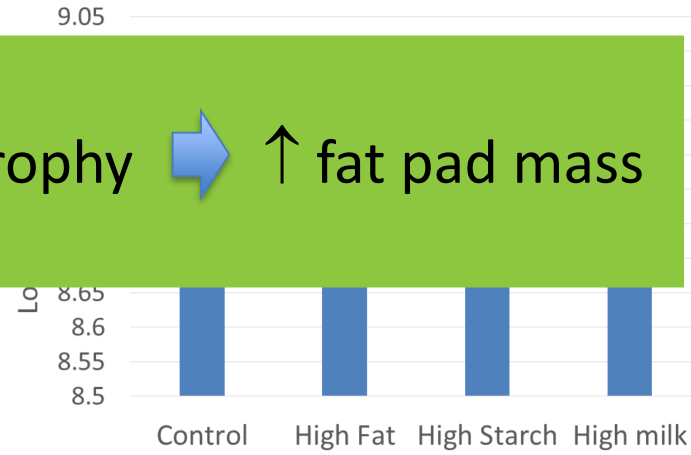
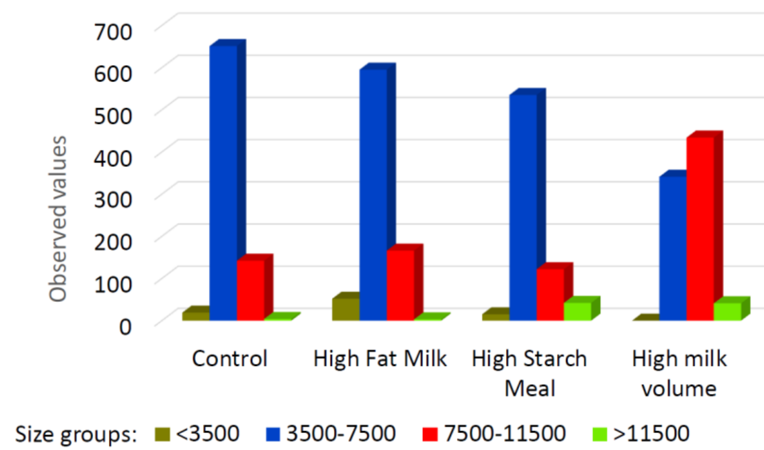
Feeding more milk (~8 vs 4L/day) ↑ mammary mass by 6 weeks of age

Calves fed more milk had larger average fat cell size (P<0.001)

↑ Milk feeding → ↑ fat cell hypertrophy → ↑ fat pad mass







Milk replacer (MR) feeding level and composition:
Control/high starch meal: 12.5% BW MR: 22.8% protein, 20.4% fat
High fat Milk: 12.5% BW MR: 22.6% protein, 30.5% fat
High milk volume: 20% BW MR: 22.8% protein, 20.4% fat
N=12/group

Pre-weaning milk volume influences mammary fat cell size at 6 months of age but not mammary mass

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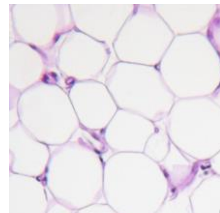
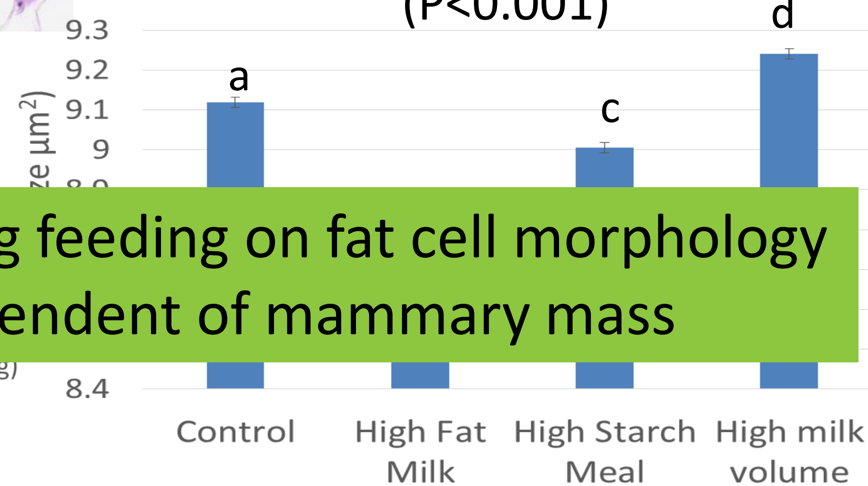
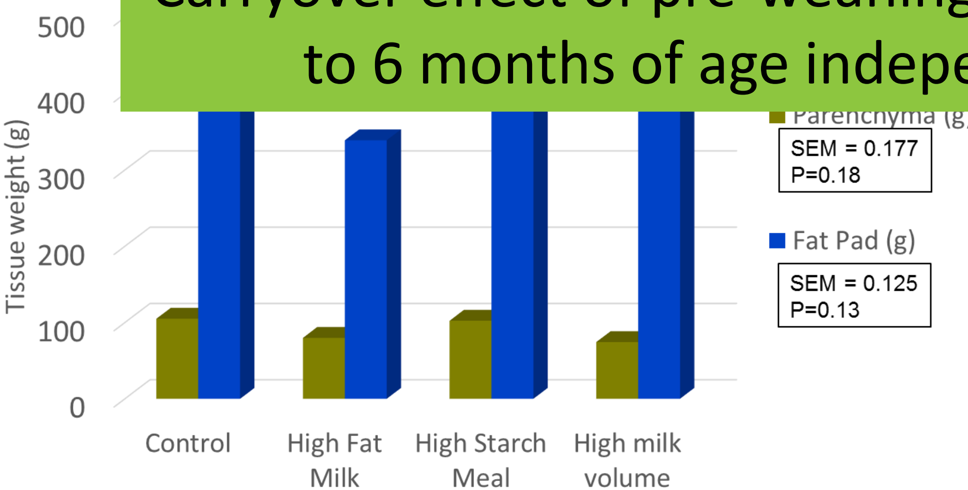


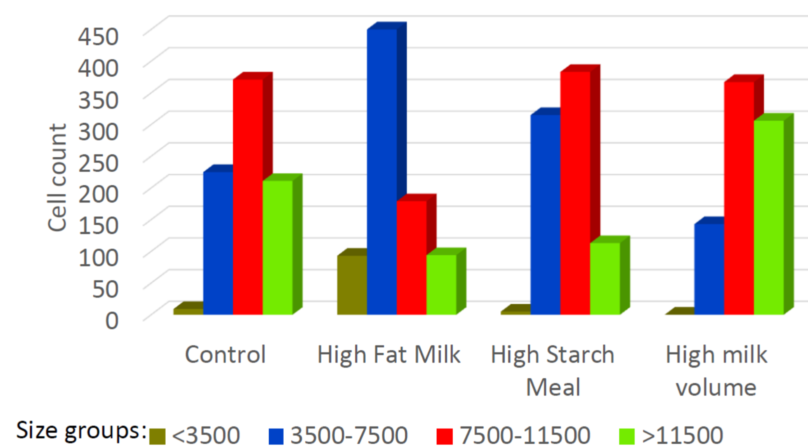
More large fat cells, and fewer small fat cells in high milk group (P<0.001)



No effect on parenchymal or fat pad mass (adjusted for body weight)

Carryover effect of pre-weaning feeding on fat cell morphology to 6 months of age independent of mammary mass



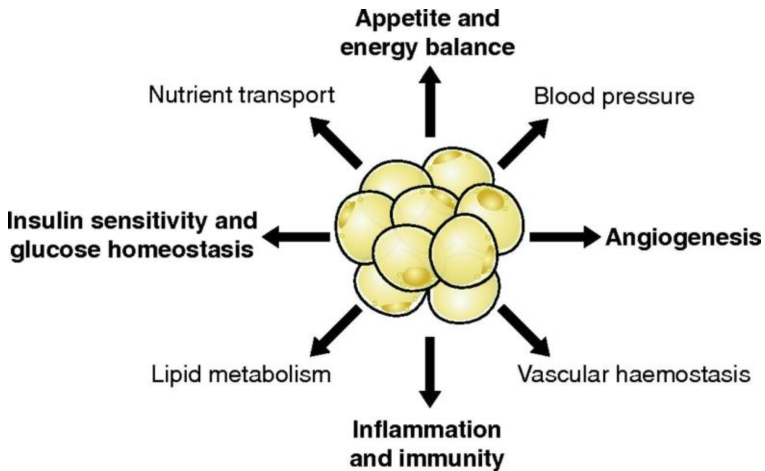


- High fat MR ↓ fat cell size and proportion of small fat cells

- More nutrients ↑ fat cell size and proportion of large fat cells
  - early allometric growth?

- Adipose tissue is an endocrine organ – adipocyte size → adipokine profiles
  Hocking et al., 2010

- Over-nutrition ↑adipocyte hyperplasia and hypertrophy
  - fatty acid dysregulation and metabolic syndromes Bozec and Hannemann 2016



Impact of nutritionally-induced changes in mammary adipocyte development in early life on adipocyte function and future mammary development and lactation?

Optimal milk feeding level?

Future directions

- Mechanisms mediating the effect of pre-weaning nutrition on mammary growth
  - *Fat pad/adipocyte and parenchymal development and crosstalk*
  - *Molecular pathways involved, e.g. mTOR, IGF-1/AA signalling*
- Critical time windows to program future milk production in ruminants
  - *Fetal period*
  - *Neonatal period*
- Impact on future milk production
  - *Targeted intervention strategies – optimal feeding levels?*
  - *Phenotyping tools/signatures for early selection*