Intestinal stem-cell organoids as experimental models to investigate feed efficiency

Acknowledgement

Host-Microbe Interactomics

Animal Breeding & Genomics

Topigs Norsvin

Animal nutrition
Feed efficiency

- Important trait
- Feed conversion ratio
- Biological mechanisms unclear & very complex
New technologies

- In vivo
- In vitro
Organoids

- 3-D structure developed in vitro
- Contains major cell types of an organ
  - Similar spatial organization
  - Recapitulating specific function(s) of the organ
- Powerful experimental models

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Aim

To show the potential of organoids as models to provide detailed molecular understanding of the underlying mechanisms of feed efficiency.

Proof of principle to compare in vitro nutrient transport in ileal organoids to in vivo data on feed efficiency in pigs.
Efficient pigs (HIGH)
FCR = 2.19 ± 0.03

Less efficient pigs (LOW)
FCR = 2.61 ± 0.04
Tissue

Ileum ~ 50 cm from ileo-caecal valve
Organoid culture system

3D organoids after ~10d culture in Matrigel

Form 2D epithelial monolayers using matrigel-coated Transwell membranes

Nutrient or immune challenge (e.g. e-coli, glucose)

Measure resistance or uptake

N = 4
LC/ mass-spectrometry

Van der Hee et al., 2018 Stem Cell Research; Figure J. Wells, HMI-WUR
Measurements

- Histology
- Resistance to commensal *E. coli*
- Transport study using glucose and amino acids
- Gene expression (RNA seq – molecular phenotypes)
Results – Histology

- Villus: crypt length
- Thickness wall
- Erosion of villi tips
- Granulocytes
- Infiltration lymphocytes
- Blunted villi

No clear differences in histology between efficient and less efficient pigs

T. Sato and H. Clevers
Results – transport study

No differences in glucose transport between pigs
Results – gene expression

- **HO (pig 4,6)**
  - High feed efficiency
  - Differential expressed - 203 genes
    - (12074 genes tested)

- **LO (pig 1,3,5,8)**
  - Low feed efficiency

- **eHO (pig 4,6)**
  - High feed efficiency – *E-coli*
  - Differential expressed - 146 genes
    - (11982 genes tested)

- **eLO (pig 1,3,5,8)**
  - Low feed efficiency – *E-coli*
  - Differential expressed - 1527 genes
    - (12118 genes tested)

**Indication:** different number of genes expressed between HIGH and LOW and between challenged and unchallenged.
Challenges

- Contamination of tissue
- Robust culture of organoids
- Validate the use of the organoids as proxy for *in vivo* performance
- High-throughput phenotyping of individual animals
Take home message

- New possibilities to understand the potential role of intestinal functions in feed efficiency
- Provide new phenotyping tools

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