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Incorporation of dairy lipids and *Lactobacillus fermentum* in infant formulas: long-term effects on intestinal permeability, mucosal immunity and metabolism in a minipig model



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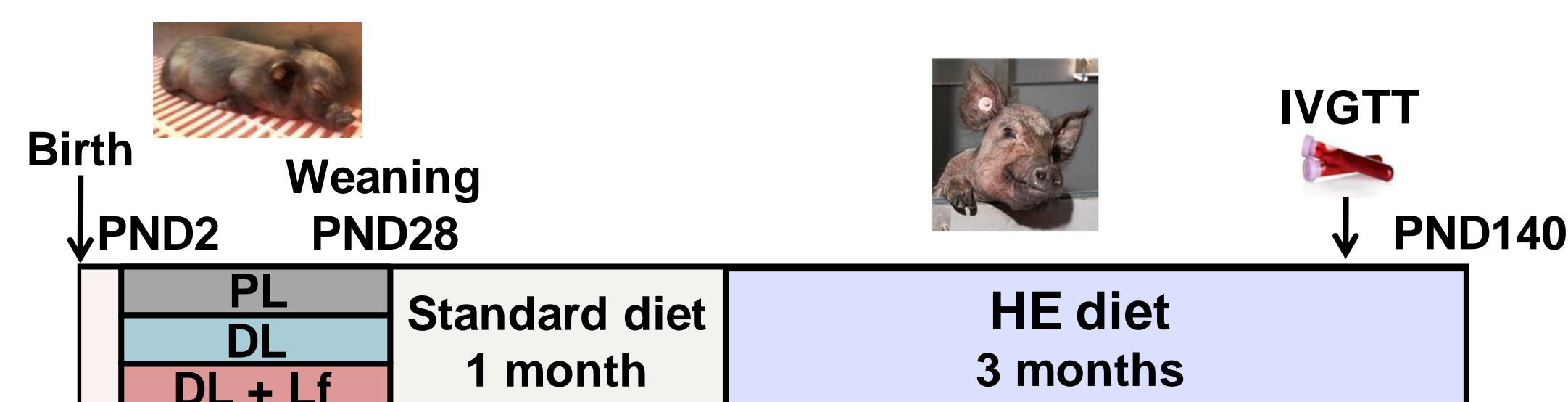


Context and objective

Incorporation of dairy lipids (DL) in infant formulas (IF) has been associated with short-term benefits on digestion, gut physiology and microbiota in a piglet model. Clinical studies showed that the probiotic *Lactobacillus fermentum* CECT 5716 (Lf) might prevent infections in infants. The objective of this study was to investigate the long-term effects of addition of both DL and Lf in IF on growth, intestinal barrier function and metabolic and immunologic status of adult Yucatan minipigs. We hypothesized that gut microbiota could be a key factor of this programming.

Methods

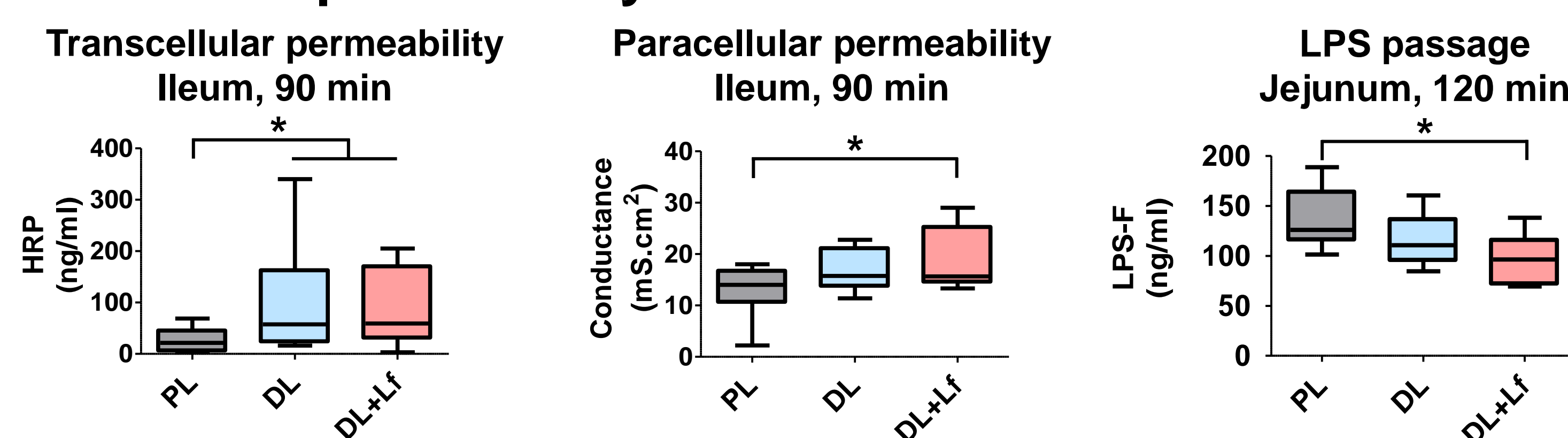
- 26 ♂ piglets received from postnatal day (PND) 2 to 28 a formula containing as lipids:
 - only plant lipids (PL)
 - a half-half mixture of PL and DL (DL)
 - a half-half mixture of PL and DL supplemented with Lf (DL+Lf).
- Pigs were subsequently fed:
 - a standard diet for 1 month
 - then challenged with a hyperenergetic diet (HE) for 3 months
 - euthanized at PND140.



- Analyses at PND140:
 - Intestinal permeability (Ussing chambers)
 - Mucosal immunity (cytokine secretion of ileal explants challenged with LPS)
 - Entero-insular axis (density of GLP-1 secreting cells, meal test, pancreas anatomy)
 - Metabolism (lipid profile, intravenous glucose tolerance test (IVGTT))
 - Gut microbiota metabolism (faecal metabolome)
 - Gut microbiota composition (16S RNA sequencing)
- Statistics:
 - ANOVA testing diet, gender and replication factors followed by post-hoc tests
 - * : $p < 0.05$ and # : $p < 0.1$
 - Data are presented as boxplot or mean \pm SEM

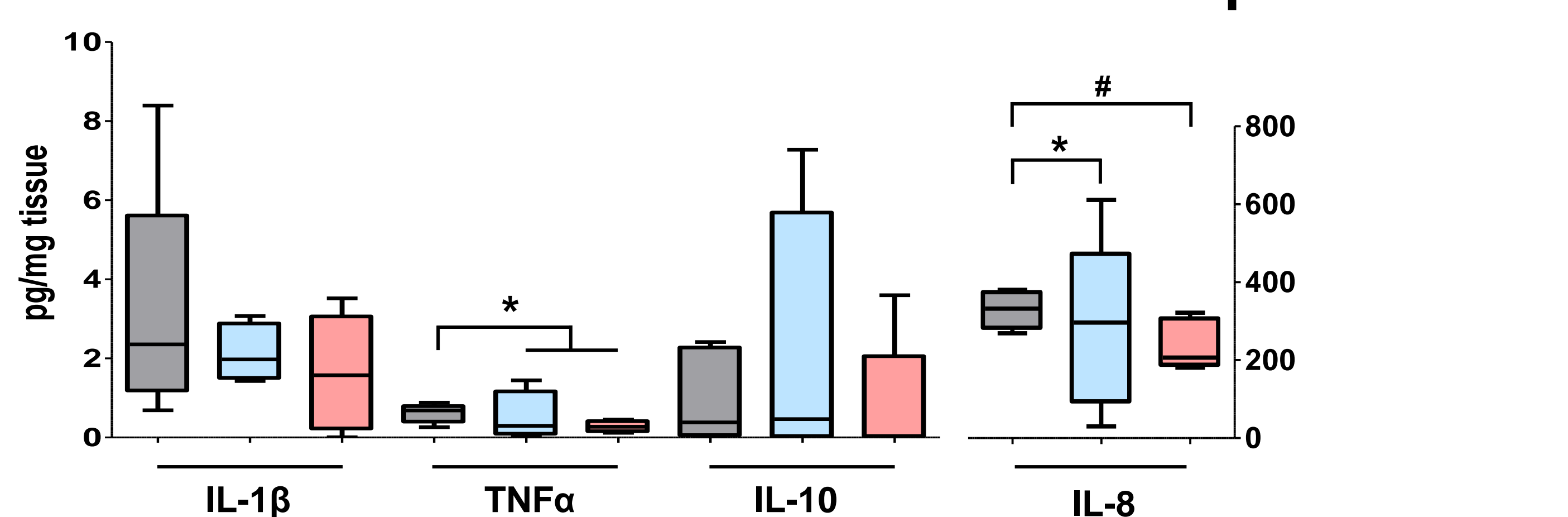
Results

1. Intestinal permeability



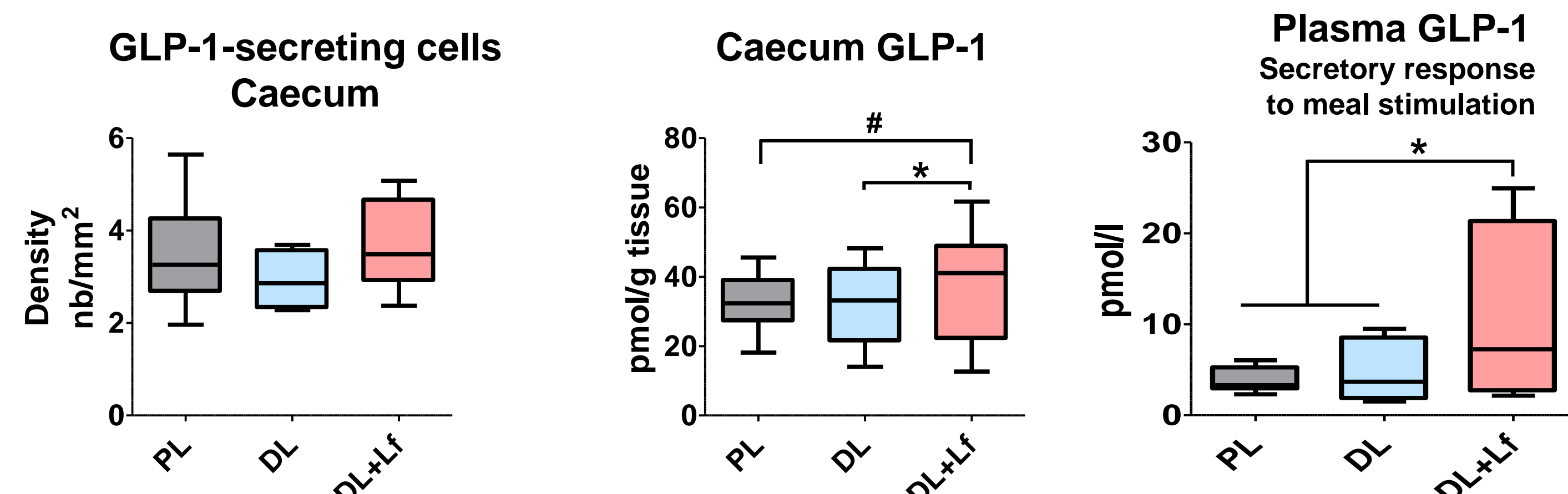
The IF composition modulated gut barrier function. Ileal trans- and paracellular permeabilities were increased in DL \pm Lf compared to PL, though jejunal LPS passage was decreased in DL+Lf compared to PL.

2. *In vitro* secretion of LPS-stimulated ileal explants



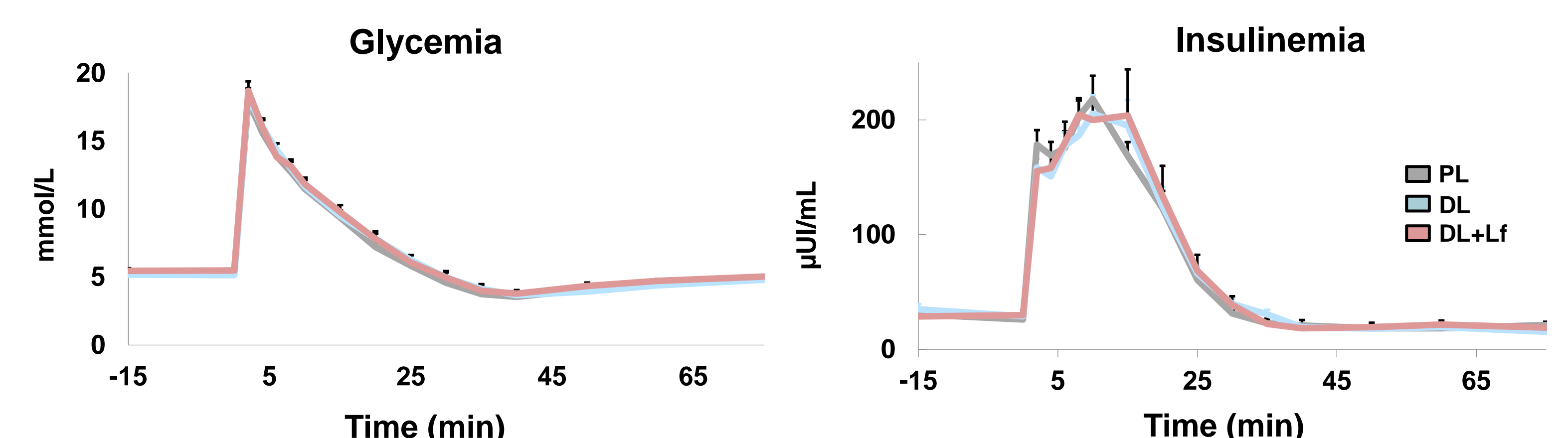
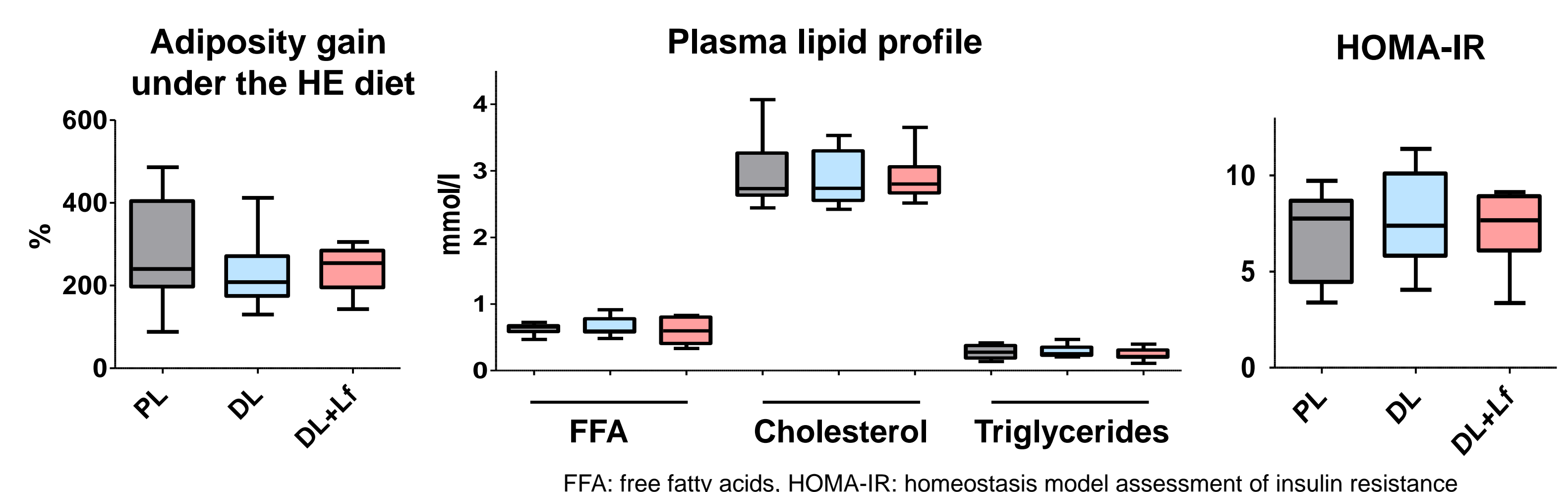
Pro-inflammatory cytokine (TNF α and IL-8) secretions of LPS-stimulated ileal explants were decreased in DL \pm Lf LPS-responders compared to PL.

3. Entero-insular axis



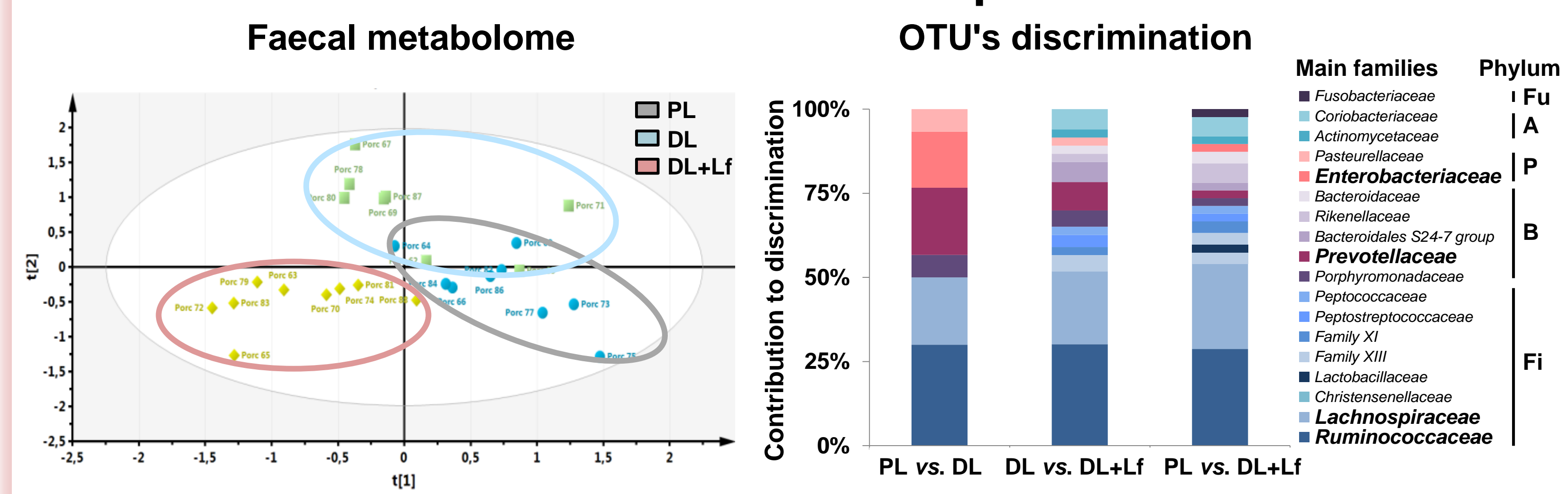
Basal and meal-stimulated GLP-1 secretory capacities were increased in DL+Lf. GLP-1 secreting cells density and pancreas anatomy (data not shown) were similar between groups.

4. Host metabolism



Growth, food intake and metabolic dysfunctions (dyslipidemia and insulin resistance) induced by the HE diet were similar between groups.

5. Gut microbiota metabolism and composition¹



Fu: Fusobacteria, A: Actinobacteria, P: Proteobacteria, B: Bacteroidetes, Fi: Firmicutes
¹ Collaboration with P. Gérard and M. Rhimi (INRA, Micalis, Jouy-en-Josas)

Gut microbiota metabolism and composition at the operational taxonomic unit (OTU) level were different between groups. It might explain the long-term effects observed on gut physiology.

Conclusion

This study highlights a long-term programming effect of early consumption of DL+Lf on intestinal epithelial barrier and endocrine function and of DL (\pm Lf) on immune orientation. These long-term effects might be mediated by changes in gut microbiota (composition and metabolism), which are different with DL alone or DL+Lf early consumption. In-depth analysis of changes in microbiota composition along with analysis of the potential mechanisms leading to the observed long-term effects are ongoing.