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Addition of dairy lipids and probiotic *Lactobacillus fermentum CECT 5716* in infant formula programs gut microbiota, epithelial permeability, immunity and GLP-1 secretion in adult minipigs

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Context and objective

Postnatal nutrition may have long-lasting metabolic and physiologic impacts in adulthood. Since gut microbiota has been identified as a key factor of this nutritional imprinting, its modulation through infant formula (IF) composition could represent a good strategy to improve the health of formula-fed infants. The addition of dairy lipids (DL) or of a probiotic strain (*Lactobacillus fermentum CECT 5716* (Lf)) have been associated with benefits in childhood, especially on gut microbiota composition. However, the interaction between DL and Lf on the short- and long-term remains unknown. The objective of this study was therefore to investigate, in a Yucatan minipig model, the long-term effects of the addition of DL and Lf in IF on adult gut microbiota and physiology.

Methods

➢ ♀♂ piglets received from postnatal day (PND) 2 to 28 a formula containing as lipids:
- only plant lipids (PL) — **PL** (n=9)
- a half-half mixture of PL and DL (DL) — **DL** (n=8)
- a half-half mixture of PL and DL supplemented with Lf (DL+Lf) — **DL+Lf** (n=9)

➢ 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 PND28 and PND140:
- Gut microbiota composition (16S RNA sequencing)
- Gut microbiota metabolism (^{1}H NMR)

➢ Analyses at PND140:
- Intestinal permeability (Ussing chambers)
- Mucosal immunity (cytokine secretion of ileal explants challenged with LPS)
- Endocrine function (density of GLP-1 secreting cells, meal test)
- Metabolism (lipid profile, glucose tolerance (IVGTT))

➢ Statistics:
- Phenotypic variables: ANOVA testing diet, gender and replication factors followed by post-hoc tests. ✱ : $p < 0.05$ and # : $p < 0.1$
- Microbiota composition: Edge R

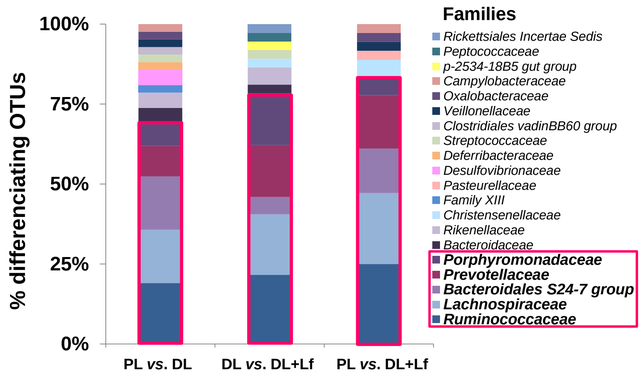
Results

1. Gut microbiota composition and metabolism

In piglets (PND28)

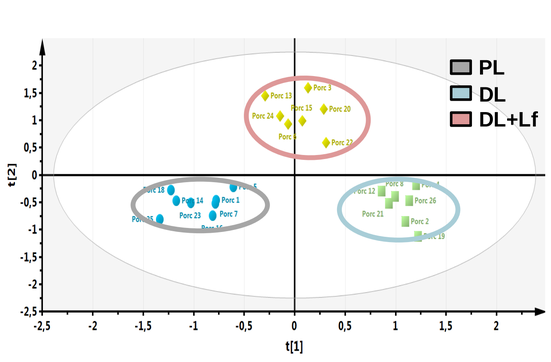
Rectal microbiota composition

2 major phyla: *Firmicutes* and *Bacteroidetes*



Rectal metabolome

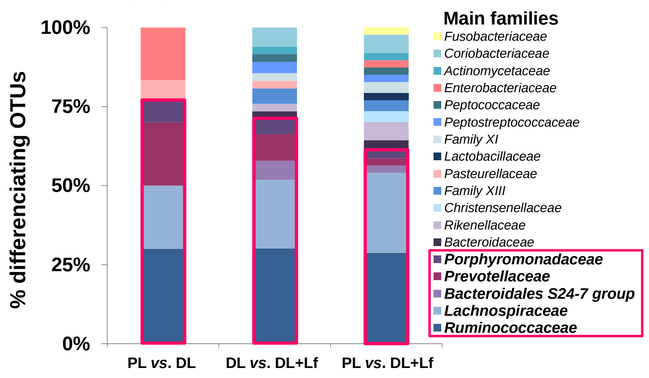
26 differenciating metabolites



In young adults (PND140)

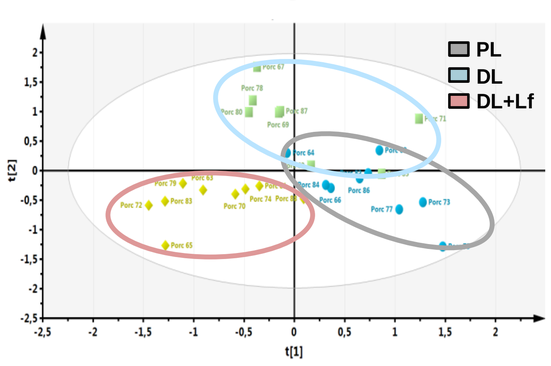
Rectal microbiota composition

2 major phyla: *Firmicutes* and *Bacteroidetes*



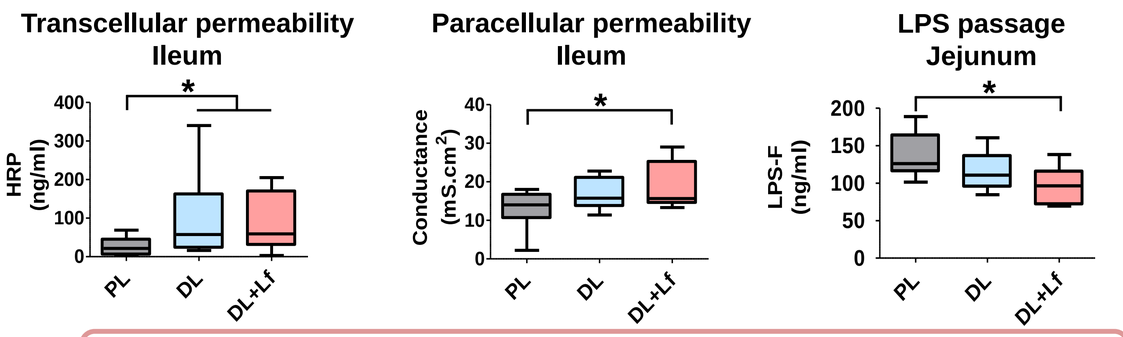
Rectal metabolome

5 differenciating metabolites



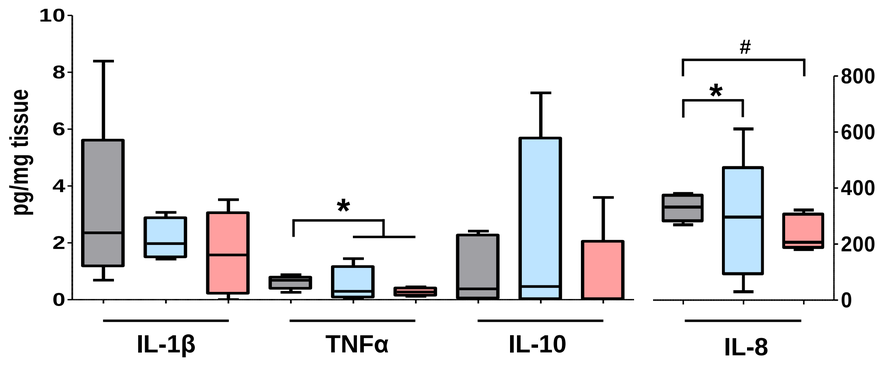
The IF composition modulated gut microbiota composition and metabolism on the short- and long-terms, implicating the same main phyla and families at both stages. The effects of DL alone or with Lf were different, the addition of Lf inducing a modulation of more families in the long-term.

2. Intestinal permeability (PND140)



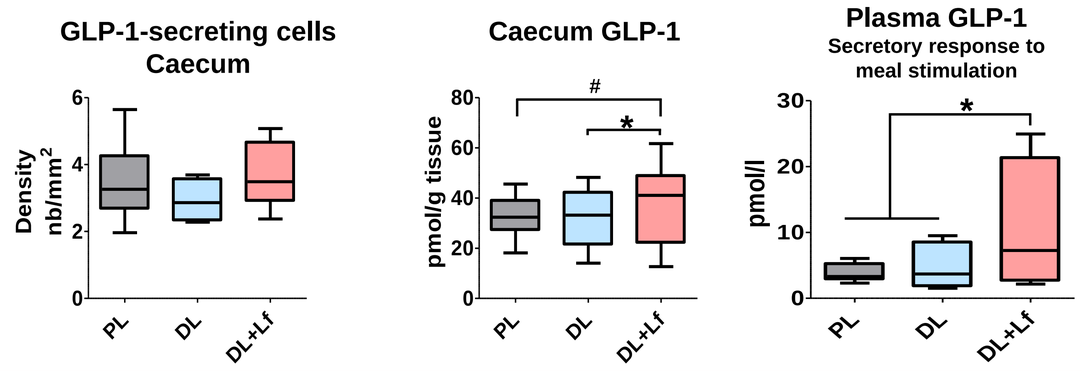
The addition of DL+Lf increased intestinal trans- and paracellular permeabilities and prevented LPS passage in the upper gut of young adult minipigs.

3. *In vitro* secretion of LPS-stimulated ileal explants (PND140)



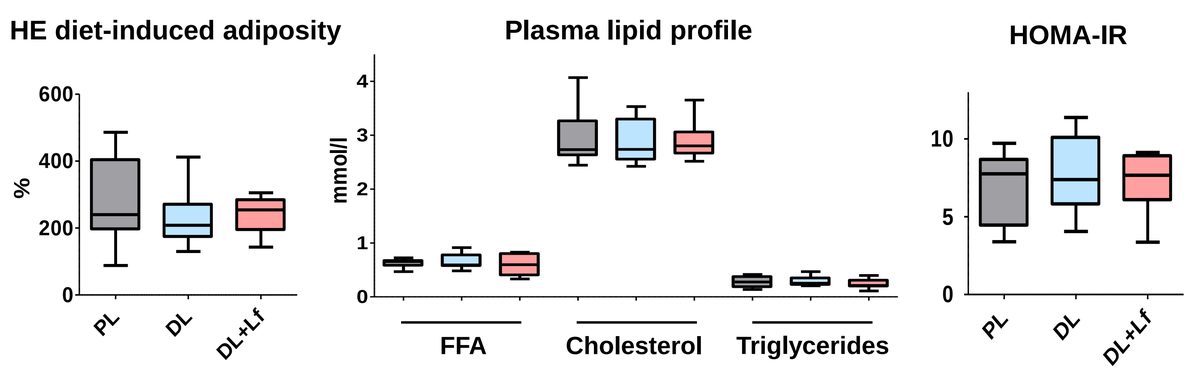
The addition of DL (± Lf) had a beneficial effect on the mucosal immunity of young adults as it decreased pro-inflammatory cytokine secretions.

4. Entero-insular axis (PND140)



The addition of Lf (+DL) had a beneficial effect on the endocrine function in young adulthood by enhancing GLP-1 basal and meal-stimulated secretory capacities.

5. Host metabolism (PND140)



FFA: free fatty acids, HOMA-IR: homeostasis model assessment of insulin resistance

The metabolic adaptations to the HE diet were similar between groups

Conclusion

This study highlights a long-term programming effect of the infant formula composition. This nutritional imprinting, mainly targeting gut microbiota and physiology (barrier, immune and endocrine functions), is different with the addition of dairy lipids alone or associated with the probiotic Lf. Dairy lipids have mainly an impact on the immune function whereas the probiotic Lf has mainly an impact on the barrier and endocrine functions. These long-term effects could be mediated by long-lasting changes in gut microbiota composition and metabolism.

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