

An intestinal transcriptome analysis in fetal pigs reveals genes involved in glucose and lipid metabolism and immunity as valuable clues of maturity at birth

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Objectives and study: Delayed physiological maturity at birth as observed in preterms compromises adaptation to extrauterine life, and accordingly impairs perinatal survival and child health. The intestine, as the major organ for nutrient absorption and the largest immune organ, fulfills its maturation during the first postnatal weeks in neonates. However, key pathways and regulators of intestinal maturity still remain poorly characterized when their identification may provide clues about adequate adaptation to enteral feeding. Our aim was to comprehensively clarify intestinal development with the objective of finding relevant regulators of intestinal maturity by using two porcine breeds, divergent in neonatal morbidity and mortality, at two gestational ages during the late fetal developmental stage (PORCINET, ANR-09-GENM-005).

Methods: Chinese Meishan (MS) and Large White (LW) breeds have been chosen as two extreme breeds for piglet mortality at birth, a better survival rate being observed in MS piglets. Nine MS and nine LW sows were inseminated with mixed semen (LW and MS) to get litters composed of both purebred fetuses (LWLW or MSMS) and crossbred fetuses (LWMS from MS sows and MSLW from LW sows). At two key time points of fetal maturation (90 and 110 days of gestation; term gestation is 114 days in pigs), umbilical cord blood and jejunum samples were collected from 63 male fetuses distributed in eight groups (two ages and four genotypes). Twenty three phenotypic variables (plasma markers of metabolisms, hormones, intestinal morphometry and enzyme activities) were analyzed using standard methods. Hybridizations of 60K porcine microarrays (Agilent technology) with intestinal RNA were analyzed with a mixed linear model and a False Discovery Rate adjusted p-value < 1% to identify genes differentially expressed in the 4 fetal genotypes and at the 2 gestational ages.

Results: Two hundred and seventy four unique annotated genes combined differential

expressions between 90 days and 110 days of gestation and between LW and MS genotypes. These differentially expressed genes (DEGs) were more particularly involved in the maturation process. In MS fetuses at day 110, functional enrichment analysis (GeneCoDis 3.0 software) disclosed overexpressed genes involved in glucose and lipid metabolisms, cell proliferation, vasculogenesis and hormone synthesis compared to MS fetuses at day 90. In LW fetuses, genes involved in immune pathways including phagocytosis, inflammation and defense processes were particularly changed in day 110 compared to day 90. The transcriptional regulator *PPARGCIA* was predicted to be an important regulator of DEGs in MS (Ingenuity® Pathway Analysis software). Fetal blood fructose level, intestinal lactase activity and villous height that were the best predicted phenotypic variables, showed correlated variances with 450 probes mostly involved in lipid metabolism, carbohydrate metabolism and cellular movement biological pathways (sparse Partial Least Square regression model, mixOmics).

Conclusion: Collectively, our findings indicate that the maturity of the intestine relies on maturation of both glucose and lipid metabolic pathways and immune phagocyte differentiation and inflammatory pathways in neonates. This process may partially be governed by *PPARGCIA*.

Disclosure of interest: None declared.

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