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Single-cell transcriptomics show a cell cycle response in ovarian mural granulosa cells of sows following a negative energy balance during lactation

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Whole-body energy status impacts reproductive outcome, with a key role for follicular granulosa cells (GCs) that determine oocyte growth and maturation. How whole-body energy stress affects GC is largely unknown.

Female pigs were fed either a standard (FF; 6.5 kg/day; n = 18) or a restricted (RES; 3.25 kg/day; n = 18) diet during the last 2 weeks of lactation until weaning and were then fully fed for 2 days after which ovaries were collected. The largest healthy follicle was identified, mural GCs were collected, total RNA was isolated, low-input RNA-seq was performed followed by data analysis and confirmatory experiments.

RES sows lost double body weight and loin muscle compared to FF sows, and ovary and follicle size were significantly smaller. RNA-seq of mural GCs revealed 2,282 differentially expressed genes (DEGs). Cell cycle was the most enriched pathway, confirmed by CDK1 immunofluorescence. In RES sows, key positive regulators of cell cycle (e.g. CCNA1, CCNA2, CCNB1, CCNB2, CCNB3, CCNE2, CDK1, CDK2, and CDK4) and proliferation biomarkers (PCNA and MKI67) were upregulated, whereas the differentiation marker CYP19A1 and the cell cycle inhibitor (CDKN1A) were downregulated. An integrated and highly correlated response of IGFBPs, AKT1, FOXO1, CDKN1A, positive cell cycle regulators, and follicle size was newly identified.

We propose a mechanism where downregulation of IGFBPs, activates the AKT-FOXO1-CDKN1A-cell cycle system, facilitating cell cycle progression. Our data suggest a catch-up growth of GCs, at the expense of differentiation. Since GCs govern oocyte development, this mechanism would explain the reduced oocyte competence at ovulation.