Epigenetic Profiling in Late Gestation Porcine Placenta Reveals Sex-Dependent Adaptations to Fetal Endocrine Status

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The placenta has crucial roles in supporting fetal development by facilitating nutrient transport and gas exchange. In pigs, as gestation progresses, structural changes in the placenta occur to accommodate the growth and increasing nutrient requirements of the developing fetus. However, the epitheliochorial porcine placenta forms a restrictive barrier that greatly limits the transplacental passage of specific molecules, including immunoglobulins and thyroid hormones. Thyroid hormones are vital for prenatal development, influencing organ differentiation and fetal growth. Beginning in early gestation, fetal pigs largely rely on autonomous thyroid hormone production rather than maternal thyroid hormone supplementation. As a result, disruptions to fetal thyroid status can negatively impact fetal growth and viability, particularly during late gestation when fetal growth is especially rapid. In swine, both pathogenic and induced hypothyroidism models have been shown to alter placental thyroid metabolism, suggesting fetal endocrine status may influence placental physiology. To better understand this relationship, placental tissues were isolated at gestation day 86 following 21-day maternal treatment with methimazole (MMI) to induce fetal hypothyroidism, and tissues were also obtained from gestational age-matched controls. We used CUT&RUN to evaluate the enrichment of histone marks (H3K4me3, H3K27ac) and the SWI/SNF central ATPase BRG1 in placental tissue, which, to our knowledge, represents a novel avenue of investigation in this area. Analysis of n=12 samples per treatment group (n=6 samples each from male and female fetuses per group) demonstrated differential enrichment of all three epigenetic features in placental tissue obtained from MMI-treated fetuses. Importantly, we saw that existing sex-specific differences in placental epigenetic features were exacerbated by fetal hypothyroidism, indicating that the porcine placenta is impacted by fetal endocrine status during late gestation. Taken together, these findings provide novel insights into the existence of sex-specific differences in placental chromatin state and shed light on the intricate interplay between fetal thyroid hormone levels and placental epigenome regulation.