Public Abstract

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Title:Biological Role of Conceptus Derived Factors During Early Pregnancy in Ruminants

In domestic animals, pregnancy loss during early gestation is a major cause of infertility. The majority of pregnancy loss during this time is due to errors in embryo development and is often characterized by uterine dysfunction, or asynchrony between the conceptus (embryo and surrounding trophectoderm) and uterus. During early pregnancy in sheep, uterine function is primarily regulated by hormones produced by the ovary (progesterone) and factors secreted by the developing conceptus (interferon tau or IFNT). In addition to IFNT, the conceptus as well as the uterus synthesize prostaglandins (PGs) via prostaglandin synthase two (PTGS2) and cortisol via hydroxysteroid (11-beta) dehydrogenase 1 (HSD11B1). This work tested that hypothesis that conceptus derived factors regulated gene expression changes in the trophectoderm which are essential for trophectoderm development and conceptus elongation in sheep. The hypothesis was addressed by determining the physiological roles of: (1) IFNT and interferon receptors 1 and 2 (IFNAR1 and IFNAR2) in conceptus development; (2) PG signaling through peroxisome proliferator activator receptors delta (PPARD) and gamma (PPARG) in the elongating conceptus; (3) the cortisol converting enzymes HSD11B1 and HSD11B2 in conceptus development; (4) the role of the glucocorticoid receptor (GR) in cortisol signaling during conceptus elongation. Gene knockout studies utilizing osmotic pumps to deliver morpholino antisense oligonucleotides, lentiviral transduction of shRNAs, and CRISPR/Cas9 based genome editing were used to target the elongating conceptus during elongation. Results of the studies established that: (1) IFNT is not only the maternal recognition of pregnancy signal, but is also required for conceptus elongation; (2) the IFN receptors IFNAR1 and IFNAR2 are not important for autocrine based signaling to the conceptus trophectoderm during development; (3) PPARG, but not PPARD is essential for conceptus elongation; (4) PPARG regulated pathways involved in lipid uptake and metabolism in the day 14 conceptus; (5) Regulation of intracellular cortisol levels by HSD11B1 is important for conceptus development; (6) inactivation of bioactive cortisol by the enzyme HSD11B2 is not essential for conceptus elongation, but is important for proper conceptus development; and (7) signaling through GR is not essential for conceptus development up to day 14 of pregnancy. Collectively, results of these studies support the idea that IFNT, PGs and cortisol are all important regulators of conceptus elongation during early pregnancy in ruminants. Knowledge gained from these studies provides new insight into the physiological pathways governing conceptus development and elongation and provides a foundation for future translation research that is necessary to increase fertility of domestic ruminants.