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A mathematical model of the interaction between bovine blastocyst developmental stage and progesterone-stimulated uterine factors on differential embryonic development observed on Day 15 of gestation

Paul R. Shorten,*[1] Anita M. Ledgard,* Martyn Donnison,* Peter L. Pfeffer,† Robin M. McDonald,* and Debra K. Berg*
*AgResearch Ltd., Ruakura Research Centre, Private Bag 3123, Hamilton 3240, New Zealand
†School of Biological Sciences, Victoria University of Wellington, Wellington 6140, New Zealand

ABSTRACT

A complex interaction between the developing bovine embryo and the growth potential of the uterine milieu it inhabits results in an embryo capable of developing past the maternal recognition stage and on to a successful pregnancy. Previously, we observed variation in the lengths of embryos recovered 8 d after bulk transfer of Day 7 in vitro-produced (IVP) blastocysts into the same uterus. Potential causes of the differential embryonic growth were examined and modeled using 2 rounds of bulk (n = 4–6) IVP transfers and recovery of these embryos 8 d later. Morphological and gene expression measurements of the embryos were determined and the progesterone concentration of the cows was measured throughout the reproductive cycle as a reflection of the status of the uterine environment. These data were used to develop and evaluate a model that describes the interaction between the uterine environment and the growth rate of the developing embryo. Expression of 6 trophectoderm genes (*IFNT*, *TKDP1*, *PAG11*, *PTGS2*, *DKK1*, and *PDPN*) was correlated with conceptus length. The model determined that if the embryo develops to blastocyst stage, the uterine environment, driven by progesterone, is a more important component than blastocyst size in the stimulation of embryonic growth rate to ensure adequate interferon tau (IFNT) for pregnancy recognition. We detected an effect of Day 7 progesterone on the expression of all 6 genes, embryonic disc size, and trophectoderm length on Day 15. We also found effects of embryo transfer size on trophectoderm length and expression of *IFNT* and *PAG11* on Day 15. Lower energy balance over the period from transfer to recovery was associated with reduced embryo growth to Day 15, and this effect was independent of progesterone. Energy balance also affected expression of *PDPN* and *TKDP1* on Day 15. We observed an effect of energy balance from transfer to recovery on embryo survival in cows with partial embryo losses, where embryo factors dominate embryo survival, with cows with greater energy balance having lower embryo losses. This effect was independent of energy balance 40 d before transfer and suggests that energy balance has direct, immediate effects on the embryo and maternal environment during this period. Furthermore, energy balance effects on embryo survival in cows with partial embryo losses were largely mediated by expression of *TKDP1*, *PAG11*, and *PDPN*. These results provide candidate signaling pathways for the effect of progesterone and energy balance on embryo growth and survival.
Key words: embryonic disc, embryonic growth model, interferon tau, uterine environment

INTRODUCTION

The developing ruminant conceptus is dependent on maternally derived factors including amino acids, cytokines, glucose, and growth factors present in the uterine luminal fluid for its growth and development beyond Day 7. These maternally derived factors are crucial for successful elongation of the blastocyst and have not yet been replicated successfully using in vitro production (**IVP**) techniques (Brandão et al., 2004; Machado et al., 2013). The importance of uterine gland secretions into the histotroph has been demonstrated by the ablation of uterine gland development in the perinatal ewe, resulting in a maternal environment in which embryos fail to successfully elongate (Gray et al., 2002). The environment of the developing embryo is an essential regulator of interferon tau (**IFNT**) production, which overrides luteolytic mechanisms to allow the establishment and maintenance of pregnancy (Spencer et al., 2007). Early in the estrous cycle, the secretion of uterine proteins into the lumen changes as the hormone profile changes. Progesterone is one of the main regula-

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[1]Corresponding author: paul.shorten@agresearch.co.nz

tors of the genes expressed in the endometrium that are involved in the preparation of the uterus during early pregnancy (Bazer et al., 1979; Spencer et al., 2004) and this is reflected in the protein expressed in the uterine histotroph (Ledgard et al., 2012; Forde et al., 2014). In beef heifers, elevation of progesterone concentrations on Days 5 and 7 after estrus results in an increase in the size of the conceptus at Day 16 (Garrett et al., 1988; Carter et al., 2008) and it appears that the altered histotroph composition produces this effect rather than a direct effect of progesterone on the embryo (Clemente et al., 2009). Lactating cows have lower serum progesterone concentrations throughout the cycle compared with heifers (Rizos et al., 2010), possibly because of the reported faster rate of metabolism of progesterone in lactating cows compared with nonlactating cows (Sangsritavong et al., 2002). Embryonic mortality due to the uterine environment is as high as 13% for cows compared with 3% in heifers (Berg et al., 2010). Several factors other than progesterone may influence the difference in uterine luminal fluid composition, including nutrition and metabolic state of the animal (Roche et al., 2011). The combination of these factors will result in a downstream modulating effect on uterine protein levels present in the luminal fluid, which can be specific to individual animals (Ledgard et al., 2011). One mode of action of the uterine influence may be on the metabolic growth rate of embryos, because it has been shown that Day 18 embryos recovered from heifers had more active biosynthetic pathways than those derived from lactating cows (Valour et al., 2014).

However, the embryo also contributes to the complexity of events that occur during preimplantation and this ultimately affects pregnancy outcome (Ulbrich et al., 2012). Approximately 5% of embryos die because of gross chromosomal abnormalities that prevent development (Peters, 1996), and oocyte developmental competence varies depending on which category of follicular environment they have been derived from (Pavlok et al., 1992; Lonergan et al., 1994). As early as 1980, researchers reported variable length in bovine embryos recovered 15 d after superovulation from the same heifer (Betteridge et al., 1980). Those authors retransferred embryos with a range of sizes to recipients, which resulted in pregnancies from embryos as small as 2 mm on transfer to the largest (18 mm) embryo transferred; however, the input of the recipient was not well defined. We have noted in our previous studies that a range of conceptus lengths may be recovered from the same cow on gestational Day 14 or 15 from bulk transfer of IVP blastocysts (Berg et al., 2010). The trophectoderm can continue to elongate in vivo even without the embryonic disc, as demonstrated in a study where the discs were excised from tubular conceptuses before their transfer to a recipient (Fléchon et al., 1986). However, those cultured in vitro did not elongate further. As the amount of IFNT secreted by the embryo is consistent with the size of the trophectoderm tissue (Robinson et al., 2006), the amount of IFNT present in the uterus available to signal pregnancy is therefore dependent on the growth rate of the embryo.

In this study, we examined in detail the development of embryos on Day 15 using bulk transfer (n = 4 to 6 per cow) of Day 7 IVP blastocysts. Developmental differences between those nurtured in different maternal environments and any disparate development of those supported in an identical uterine environment (i.e., the same cow) were examined. The conceptus length, its trophectoderm gene expression, and embryonic disc development were compared to determine developmental variability. A mathematical model is proposed to calculate the early pre-attachment embryonic growth rate, encompassing both the embryonic and maternal factors.

MATERIALS AND METHODS

Animals

All experimental procedures were undertaken in accordance with the regulations of the New Zealand Animal Welfare Act of 1999 under Ruakura Animal Ethics Committee approval AE12652. High breeding value Friesian cows (n = 37) in their second lactation were used to compare IVP embryo development at gestational Day 15 within the same uterine environment. The cows were maintained at the AgResearch Tokanui Farm under normal pastoral "best farm practice" grazing herd management plus silage as required to achieve a BCS of 5 (10-point scale) before calving. Following calving, the cows were subjected to various milking frequencies (0, 1, or 3 times per day), with feed intake and exercise manipulated to reduce the variation in BCS throughout the experiment. The animals were under veterinarian supervision throughout the experiment.

Sequential Embryo Transfer and Recovery

At approximately 28 to 30 d postpartum, the estrous cycles of the cows were synchronized using controlled internal drug releasing (CIDR) inserts (Zoetis, Auckland, New Zealand). The CIDR was inserted for a total of 12 d, with a single injection of a prostaglandin $F_{2\alpha}$ analog (2 mL of 250 mg/mL cloprostenol sodium; Estroplan, Parnell Technologies, Alexandria, Australia) given on d 8. At the time of CIDR removal, cows were tail-painted and observed for estrous behavior, and an initial IVP transfer was performed on Day 7 after standing estrus

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