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Maternal organism and embryo biosensoring: insights from ruminants

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ABSTRACT

In terms of contribution to pregnancy, the mother not only produces gametes, but also hosts gestation, whose progression in the uterus is conditioned by early events during implantation. In ruminants, this period is associated with elongation of the extra-embryonic tissues, gastrulation of the embryonic disk and cross-talk with the endometrium. Recent data have prompted the need for accurate staging of the bovine conceptus and shown that asynchrony between elongation and gastrulation processes may account for pregnancy failure. Data mining of endometrial gene signatures has allowed the identification of molecular pathways and new factors regulated by the conceptus (*e.g.* FOXL2, SOCS6). Interferon-tau has been recognised to be the major signal of pregnancy recognition, but prostaglandins and lysophospholipids have also been demonstrated to be critical players at the conceptus–endometrium interface. Interestingly, up-regulation of interferon-regulated gene expression has been identified in circulating immune cells during implantation, making these factors a potential source of non-invasive biomarkers for early pregnancy. Distinct endometrial responses have been shown to be elicited by embryos produced by artificial insemination, *in vitro* fertilisation or somatic cell nuclear transfer. These findings have led to the concept that endometrium is an early biosensor of embryo quality. This biological property first demonstrated in cattle has been recently extended and associated with embryo selection in humans. Hence, compromised or suboptimal endometrial quality can subtly or deeply affect embryo development, with visible and sometimes severe consequences for placentation, foetal development, pregnancy outcome and the long-term health of the offspring.

1. Introduction

In mammals, the birth of a viable and healthy progeny involves a sequence of complex biological processes and several critical points that have to be successfully overcome. In terms of the contribution to pregnancy (onset, progress, and issue), the male differs from the female. Indeed, whereas the paternal contribution is represented by the sperm, the mother not only produces the gametes (oocyte), but also hosts the whole gestation in a reproductive tract until term. Nutrition, stress, infections or endocrine disruptors have been identified as factors that affect gamete quality and fertilisation, journey of the early

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embryo through the oviduct, cellular interactions between endometrium and hatched blastocyst or conceptus, foeto-placental development or parturition (Fleming et al., 2004; Leroy et al., 2008). In addition, assisted reproductive technologies (ART) associated with embryo transfer have been shown to alter the biological properties of the embryo with a subsequent impact on the later stages of pregnancy (Sinclair, 2008). Therefore, an inadequate maternal compartment and/or suboptimal quality of the embryo may have an impact on the two-way communication between mother and embryo, precluding completion of successful pregnancy and affecting the long-term health status of the offspring (Douglas, 2011).

In vitro production of embryos and embryo transfer have demonstrated the oviduct to be a dispensable organ for supporting progression of pregnancy to term. Until now, despite several attempts to maintain early and late foetal life outside the uterus (Bulletti et al., 2011), no surrogate biological or artificial system has been derived for the uterus. Under normal physiological conditions, the uterus and its internal part, referred to as the endometrium, constitute the maternal site for embryo implantation. The implantation process has been recognised to be a critical step of pregnancy that is associated with a high rate of embryo loss in all mammalian species studied so far. As an illustration, whereas the calving rate of pregnancy has been estimated to be 40% in Holstein–Friesian dairy cows, more than 70% of pregnancy failure has been associated with embryo death occurring during the early and late pre-implantation period (Diskin and Morris, 2008). Obviously, this poor reproductive performance represents a major cause of economic loss that prompts the need for a thorough investigation of the events leading to embryo mortality during the establishment of pregnancy. External events related to the environment or intrinsic maternal features may affect the biological functions of maternal organs or tissues that will in turn have an impact on endometrial physiology (Fig. 1). As the ultimate and unique biological layer facing the implanting embryo in normal early pregnancy, the endometrium drives the development of the embryonic disc and extra-embryonic tissues (Hue et al., 2007). Complementary to this driver feature, recent data based on *in vitro* embryo manipulations have unveiled an unexpected biosensoring property of the endometrium (Sandra et al., 2011). While focussing on bovine and ovine species, this review aims to present recent data that have explored how the maternal environment exhibits global and subtle reactions to the conceptus at the local and systemic levels during early pregnancy in physiological or perturbed situations.

2. Brief overview of early pregnancy events in ruminants

In ruminants, the bicornuate uterus is covered with the endometrium, displaying two specific areas, namely the caruncles and the intercaruncular areas (Chavatte-Palmer and Guillomot, 2007; Fig. 1). The caruncles represent aglandular structures of limited size and are distributed over the endometrial surface. The intercaruncular areas are large and contain the endometrial glands, which produce histotroph, a collection of numerous and diverse factors including cytokines and growth factors (Spencer and Bazer, 2004). Upon oocyte fertilisation and after hatching, the extra-embryonic tissue of the conceptus undergoes a progressive and critical elongation phase (Degrelle et al., 2005) before implanting at days 15–16 post-oestrus in the sheep and the goat (gestation period: 5 months) or at days 19–20 post-oestrus in cattle (gestation period: 9 months). Although a decidual-like process (related to haemochorial implantation) has been reported in sheep (Johnson et al., 2003), ruminant implantation is characterised by the apposition and then the adhesion between the trophectoderm and the uterine luminal epithelium, ultimately forming a synepitheliochorial placenta (Bazer et al., 2009).

The anatomy of the ovine uterus is advantageous for identifying the local endometrial reaction triggered by embryo-related factors *in vivo*. In the ovine model of unilateral pregnancy, the conceptus is confined to the uterine horn ipsilateral to the corpus luteum by placing a ligature proximal to the uterine body (Bazer et al., 1979). By comparing the gravid and the non-gravid horns, the paracrine impact of conceptus-secreted factors on the endometrium can be dissociated from their endocrine actions. In this model, dynamic changes of endometrial T lymphocyte populations were reported to be independent from embryo secretions (Majewski et al., 2001), whereas the localisation of macrophages was affected by the presence of the conceptus (Tekin and Hansen, 2004). At the molecular level, Sandra et al. (2005) reported the paracrine influence of the conceptus on the endometrial expression of SOCS genes, a family of intracellular factors displaying major functions in the negative control of cytokine signalling pathways.

Although the first steps of uterine remodelling and the timing of the window of implantation are programmed by maternal hormones independently from the presence of the embryo, successful pregnancy will require embryo recognition by the maternal organism with a critical contribution of the uterine reaction. This reaction is promoted by the production of embryonic factors that are indispensable for initiating the implantation process through the establishment of permanent cellular interactions between the trophectoderm and the endometrium (Guillomot, 1995). Embryo-derived signals vary according to mammalian species and they have been abundantly reviewed, particularly in ruminants for which the major signal of pregnancy recognition has been identified as a type I interferon (Spencer et al., 2008; Dorniak et al., 2013b). The production of this interferon (interferon-tau; IFNT) is unique as it is secreted by trophectoderm cells during the elongation phase and then stops when trophectoderm cells appose the luminal endometrial epithelium. IFNT is crucial for maternal recognition through the inhibition of endometrial prostaglandin-F2 alpha secretion, thus preventing luteolysis, an indispensable step for maintaining P4 luteal secretion (Martal et al., 1998; Roberts et al., 2008). Nevertheless, IFNT is not the only factor of embryo origin affecting uterine physiology and other molecules have been identified. Indeed, at the conceptus–endometrial interface of ruminants, two main categories of lipid mediators have been highlighted, namely cyclooxygenated derivatives