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Review article

The role of placental MHC class I expression in immune-assisted separation of the fetal membranes in cattle

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ABSTRACT

The bovine fetus, like that of other species, is a semi-allograft and the regulation of materno-fetal alloimmunity is critical to prevent its immunological rejection. In cattle, a materno-fetal alloimmune response may be beneficial at parturition. It is hypothesized that upregulation of major histocompatibility complex (MHC) class I on the fetal membranes toward the end of gestation induces a maternal alloimmune response that activates innate immune effector mechanisms, aiding in the loss of the adherence between the fetal membranes and the uterus. Loss of fetal–maternal adherence is pivotal for the timely expulsion of the fetal membranes and the absence (or reduction) of the maternal immune response may lead to retained fetal membranes, a common reproductive disorder of cattle. Currently, there is no effective treatment for retained fetal membranes and a better understanding of materno-fetal alloimmune-assisted separation of the fetal membranes may lead to novel targets for the treatment of retained fetal membranes. In this review, the regulation of materno-fetal alloimmunity during pregnancy in cattle, with a focus on placental MHC class I expression, and the importance of maternal alloimmunity for the timely separation of the fetal membranes, are discussed.

1. Introduction

The bovine fetus inherits and expresses paternal antigens and is thus semi-allogeneic to the maternal immune system. Preventing immunological rejection of the fetus is, therefore, critical for a successful pregnancy. Maternal antibodies against paternal alloantigens are induced in up to 64% of multiparous cattle and can be detected as early as the second trimester of gestation (Hines and Newman, 1981), showing that the materno-fetal immune response is regulated, rather than suppressed, and is normally not harmful to the fetus. In cattle, delayed expulsion of the fetal membranes, a common reproductive disorder, is associated with a reduced maternal (allo)immune response (Benedictus et al., 2011, 2012; Gunnink, 1984b; Joosten et al., 1991), suggesting that at parturition a materno-fetal alloimmune response may be beneficial for the separation of the fetal membranes. The regulation of materno-fetal alloimmunity

Abbreviations: MHC, major histocompatibility complex; NC-MHC class I, non-classical MHC class I; BNC, binucleate cells; RFM, retained fetal membranes; ECM, extracellular matrix; MMP, matrix metalloproteinases; TIMP, tissue inhibitors of MMPs; CR, coefficient of relationship.

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during pregnancy in cattle, with a focus on placental MHC class I expression, and the importance of maternal alloimmunity for the timely separation of the fetal membranes, are discussed.

2. Placental MHC class I expression and regulation of materno-fetal alloimmunity during pregnancy

There are three basic mechanisms preventing immunological rejection of the fetus (Bainbridge, 2000; Lynge et al., 2014):

(i) Anatomical separation of the fetus from the maternal immune system;
(ii) Down-regulation of alloantigen expression by the fetus;
(iii) Regulation of the maternal immune response in the uterus.

Care should be taken in extrapolating findings on the regulation of materno-fetal immunity during pregnancy from other species to cattle. There are large differences in placental morphology between species and the common ancestor of species with long gestation periods (e.g., horse, cattle, and humans) had a short gestation period. Therefore, mechanisms to regulate materno-fetal immunity during pregnancy (for a prolonged time) have evolved separately in these lineages and are likely to be species-specific (Bainbridge, 2000).

In the bovine placenta fetal trophoblasts and maternal endometrium form a continuous epithelial lining across the whole placenta (Fig. 1) (Schlafer et al., 2000). Specialized structures called placentomes form through interdigitation of maternal (caruncle) and fetal (cotyledon) epithelium, thereby increasing the surface area for the exchange of waste and nutrients (Schlafer et al., 2000). Bovine placental histology is in strong contrast to the human placenta, where fetal trophoblasts are directly in contact with maternal blood and extravillous trophoblasts that invade the uterine tissue and reshape maternal blood vessels (Gude et al., 2004). The anatomy of the bovine placenta ensures that there is minimal contact between the maternal immune system and fetal cells.

Allogeneic MHC class I is highly immunogenic and in several species it has been shown that MHC class I is down-regulated on fetal trophoblasts, e.g., humans, horse and pig (Bainbridge, 2000). In cattle MHC class I expression on fetal trophoblasts is down-regulated in early pregnancy, but toward mid-gestation expression becomes apparent in interplacentomal regions and rises toward the end of gestation (Davies et al., 2000; Low et al., 1990). In the placentomes, at the area of most intimate contact, there is no MHC class I expression on the trophoblasts (Chavatte-Palmer et al., 2007; Davies et al., 2000; Low et al., 1990). In an elegant study by Davies et al. (2006) it was shown that interplacentomal trophoblasts transcribe very high levels of non-classical MHC class I, indicating that a proportion of the MHC class I proteins expressed by bovine trophoblasts is non-classical. Ellis et al. (1998) detected transcription of MHC class I in late gestation placentome-derived trophoblasts, but could not detect the expression of MHC class I with ILA88, a monoclonal antibody that is pan-specific for bovine MHC class I, and hypothesized that this could reflect the expression of non-classical MHC class I (NC-MHC class I). Since there are no bovine NC-MHC class I-specific antibodies, it is currently impossible to differentiate classical and non-classical MHC class I protein expression in the bovine placenta. In human pregnancies HLA-G, a NC-MHC class I, is highly expressed on trophoblasts, both on the cell membrane and in soluble form, and is believed to be of importance for immune regulation, suppression, and tolerance induction at the fetal–maternal interface (Lynge et al., 2014). Davies et al. (2006) found multiple splice variants of one non-classical allele, including a variant with a deletion of the transmembrane domain, indicating that soluble bovine NC-MHC class I may be expressed. It is probable that NC-MHC class I expression on bovine trophoblasts plays a similar role to HLA-G in humans and that expression of NC-MHC class I and restricted expression of classical MHC class I by the fetus contribute to the regulation of maternal immunity.

Binucleate cells (BNC), specialized cells formed from uninucleate trophoblasts and unique to ruminants, can migrate to the endometrium and fuse with maternal cells, temporarily forming trinucleate cells (Fig. 1) (Schlafer et al., 2000; Wooding, 1992). BNC produce an array of secretory molecules, including placental lactogen,

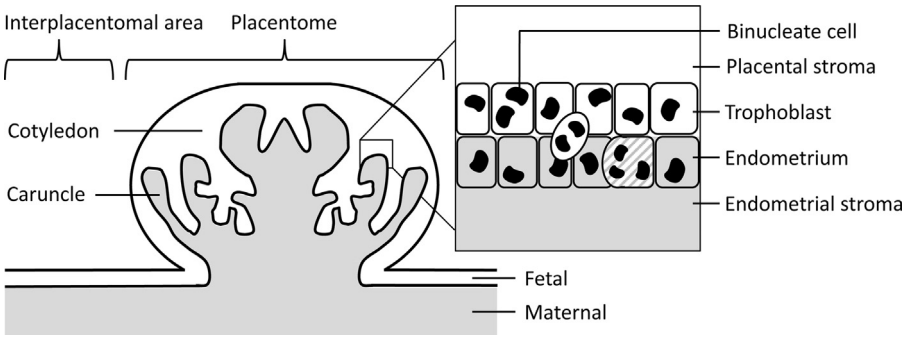

Fig. 1. Bovine placentomes. Placentomes are formed through interdigitation of maternal (caruncle) and fetal (cotyledon) tissue. The apposition of fetal trophoblasts to the maternal endometrium forms a continuous epithelial lining across the placenta. Binucleate cells, specialized trophoblasts, can migrate to the maternal side and may fuse with endometrial cells, forming trinucleate hybrid cells (shaded).