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Embryo maternal immune interactions in cattle

T. Fair[1]

School of Agriculture and Food Sciences, University College Dublin, Ireland.

Abstract

Mammalian embryo implantation requires the priming of the maternal immune system, but, not the provocation. There are many examples of conditions where a disturbed or aberrant immune profile during embryo implantation leads to pregnancy loss. However, these studies are primarily associated with human and mouse species; data is generally limited for cattle and livestock. Most available information centres on the endometrial response to interferon tau (IFNT), a type I antiviral cytokine, which is the maternal recognition factor for cattle and sheep. Interferon tau secretion by the embryo and detection by the dam is critical to corpus luteum (CL) maintenance and pregnancy retention. However, the large volume of bovine endometrial and conceptual transcriptomic data highlights a broader more integral role of the maternal immune system in the establishment of pregnancy in cattle. When taken together with available immunohistochemistry and flow cytometry data from livestock, mouse, and human, a profile of immune cell involvement from ovulation to conception and placentation emerges. The key events of pregnancy establishment in cattle and the involvement of the maternal immune system will be discussed.

Keywords: Cow implantation pregnancy immune-system embryo.

Introduction

The maternal immune system plays a critical role in mammalian embryo implantation. Successful establishment of pregnancy requires the activation of a controlled immune response that is simultaneously responsive and tolerant towards paternal antigens and the semi-allogenic embryo. The discipline of Reproductive Immunology has received considerable attention from a human clinical point of view and much data has been gathered from patients and generated from various mouse and *in vitro* model systems. In contrast, information from cattle mostly revolves around the endometrial response to the maternal recognition factor for cattle and sheep, the type I antiviral cytokine, interferon tau (IFNT), detection of which by the dam is critical to corpus luteum (CL) maintenance and the establishment of pregnancy. The greatest source of information has come from the large volume of bovine endometrial and conceptal transcriptomic data that has been generated in the past decade. The emerging knowledge clearly indicates that regardless of specificities in placentation physiology, an appropriate maternal immune response is just as critical to the establishment of pregnancy in cattle as it is in human and rodents.

In cattle, the first three to four cell cycle divisions post fertilization occur in the oviduct, such that the embryo enters the uterus on approximately day 4 post fertilization. There it undergoes a number of cell divisions to form the morula which, after differentiation, forms a blastocyst consisting of the inner cells mass (which will eventually give rise to the embryo/foetus) and an outer cell mass consisting of trophectoderm cells which ultimately give rise to the placenta. Up to this stage, the embryo is encased in the glycoprotein shell, the zona pellucida. Therefore the endometrial lining is not exposed to paternal antigens again until hatching, which occurs from day 8 to 9 post fertilization. Transcriptomic analysis of the bovine endometrium during this early stage of pregnancy indicates little or no change in gene expression in response to the zona-enclosed blastocyst stage embryo (Forde *et al*., 2011; Forde and Lonergan, 2012). Once hatched, the blastocyst forms an ovoid-shaped conceptus between days 12-14 and the elongation process begins. Elongation entails rapid proliferation of the conceptus trophectoderm cells, reaching 3-4 mm or more in length by day 14 (Randi *et al*., 2015), and 25 cm or more in length by day 17. As the embryo elongates, the trophectoderm and endometrial luminal epithelium (LE) become closely apposed, see Spencer *et al*. (2007), for review. During this period the conceptus relies on maternal secretions, collectively termed histotroph, for survival (Bazer, 1975). In contrast to mouse and human species, implantation in cattle is non-invasive. It is characterized by a superficial attachment and adhesion of the trophectoderm to caruncular and intercaruncular areas, commencing about day 19 (see Brooks *et al*., 2014), for review. During implantation, bovine trophectoderm cells form binucleate cells (BNCs) as well as trinucleate cells (TNCs), TNCs are products of fusion between binucleate cells and uterine epithelial cells (Wooding and Beckers, 1987) and are only located in the endometrium (Wooding, 1992). These multinuclear cells may play a role in implantation, contributing to the adhesion between conceptus and uterine endometrium at the placentomes. In cattle, several integrin family members (ITGs) have been characterized at the uteroplacental interface during trophectoderm attachment (MacIntyre *et al*., 2002; Pfarrer *et al*., 2003) and placentation (Pfarrer, 2006) periods and are believed to play constitutive roles. Similarly, the transmembrane glycoprotein, vascular cell adhesion -molecule (Osborn *et al*., 1989), is also regarded as a cell adhesion mediator during the processes of lymphocyte homing (May *et al*., 1993), angiogenesis

[1]Corresponding author: trudee.fair@ucd.ie
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(Ding *et al*., 2003) and allantoic membrane fusion to the chorion (Gurtner *et al*., 1995). The key events and interactions between the embryo and the dam are presented and reviewed.

The role of the embryo in the maternal immune response

Response to insemination

During transmission of seminal plasma (SP) at coitus, cells of the maternal immune system recognize various signaling constituents of semen, including interleukin (IL) -8, transforming growth factor beta (TGFB) and IFNG. In addition, sperm antigens are recognized as foreign (Robertson, 2005). The recognition of non-self initiates activation of a maternal immune response, which may ultimately confer immunological tolerance to paternal antigens that will be expressed by the embryo that develops after fertilization (Moldenhauer *et al*., 2009). The first stage of the maternal immune response is characterized by an influx of eosinophils and neutrophils to the uterine lumen. Data from mice show that chemoattractants released by these cells, such as granulocyte macrophage colony-stimulating factor (GM-CSF) and (IL) -6, attract both monocytes and dendritic cells, potentially creating an environment that regulates the inflammatory status of responding macrophages and increases expression of factors which promote early embryo development (Robertson *et al*., 1996, 2000; Robertson, 2007; Bromfield *et al*., 2014). Data from mice indicate that the absence of changes in the reproductive tract caused by SP can alter the developmental program of the developing conceptus (Bromfield, 2014). This cell-free, fluid fraction of the ejaculate is significantly diluted during semen preparation for use in AI programs, thus cows bred in this manner are only exposed to trace amount of SP. However, the relatively high pregnancy rates achieved in cattle following artificial insemination (AI) or embryo transfer (ET) suggest that maternal exposure to SP is not a critical component of the maternal immune response in cattle (Lima *et al*., 2009; Odhiambo *et al*., 2009).

Molecular response of maternal endometrium to the embryo

The presence of a rapidly elongating embryo is certainly registered by the maternal endometrium, as there is a dramatic change in global gene expression at this time (Forde *et al*., 2011). The type 1 interferon, interferon tau (IFNT), is the main signaling factor in maternal detection/recognition of pregnancy in cattle and sheep (Hansen *et al*., 1999; Choi *et al*., 2003). IFNT is secreted by the elongating conceptus, specifically the trophectoderm (Robinson *et al*., 2006). It is believed that the luminal epithelium of the uterine endometrium is the primary target for IFNT (Roberts *et al*., 1992; Imakawa *et al*., 2002); IFNT binds to a common receptor complex with two polypeptide subunits (IFNAR1 and IFNAR2; Rosenfeld *et al*., 2002). There is evidence to suggest that IFNT can reach the stroma, the uterine myometrium (Ott *et al*., 1998, Johnson *et al*., 1999, Hicks *et al*., 2003) and most likely, the circulating immune cells and the ovaries as well (Shirasuna *et al*., 2012). IFNT acts on the endometrium to stimulate the expression of genes that promote conceptus growth and development and induce uterine receptivity (Hansen *et al*., 1997, Johnson *et al*., 2000, Song *et al*., 2007; Mansouri-Attia *et al*., 2012). Candidate and global gene expression analysis revealed that a classical Type I IFN response during the peri-implantation period is induced by the conceptus/IFNT (Li and Roberts, 1994; Spencer *et al*., 2008; Mansouri-Attia *et al*., 2012;). Induced endometrial classical Type I IFN stimulated genes (ISGs) include, 2',5'-oligoadenylate synthetase 1, *OAS1* or *ISG15, MCP1* Chemokine (C-X-C motif) ligand 5; *CXCL5*, (for review, see Forde and Lonergan, (2012). The expression of several chemokines is induced in endometrial tissues including chemokine ligands 10 (*CXCL10*) and 9 (*CXCL9)*; (Nagaoka *et al*., 2003b, Imakawa *et al*., 2006). Endometrial CXCL10 attracts immune cells to the caruncular regions of the endometrium (Nagaoka *et al*., 2003a), and by acting through the CXCL10 receptor, CXCR3, this chemokine regulates TE cell migration and integrin expression (Imakawa *et al*., 2006).

Conceptus-maternal communication is vital for the successful establishment and maintenance of pregnancy, Sub-optimal communication, resulting from impairment of conceptus development and/or from abnormal uterine receptivity, contributes to a high incidence of embryonic mortality (see Lonergan and Forde, 2014, for review). Using RNA sequencing, Mamo *et al*. (2011) described the temporal changes in transcriptional profiles of the bovine conceptus from a spherical blastocyst on day 7 through days 10, 13, 16 and 19, corresponding to the formation of an ovoid conceptus, initiation of elongation, maternal recognition of pregnancy to a filamentous conceptus at the initiation of implantation on day 19. Generally, genes encoding trophoblast kunitz domain proteins, pregnancy-associated glycoproteins, cytoskeletal transcripts, heat shock proteins and calcium-binding proteins had highest expression levels at each of these stages of development (Lonergan and Forde, 2014; Mamo *et al*., 2011). Bauersachs *et al*. (2012) carried out a gene set enrichment analysis of several global transcriptomic datasets from days 15, 16, 17, 18 and 20 of the oestrus cycle or pregnancy and identified a conceptus-induced signature in the endometrium during the process of pregnancy recognition. Together with progesterone (P4), IFNT regulates endometrial gene expression necessary for the establishment of the proper uterine environment during the implantation period (Klein *et al*., 2006). A panel of approximately 30 genes was identified as expressed on day 16 as part of the early endometrial response to the conceptus and may represent early endometrial markers of a viable pre-implantation conceptus (Bauersachs *et al*., 2006, Mansouri-Attia *et al*., 2009a), reviewed by Lonergan and Forde (Forde and Lonergan, 2012). Although most data demonstrates that the main molecule affecting the

endometrium is IFNT, additional conceptus secreted molecules, including prostaglandins (PG; Dorniak *et al*., 2012, Spencer *et al*., 2013) and cortisol (Dorniak *et al*., 2013b), also act on the endometrium. An additional, but critically important action of IFNT, is the attenuation of endometrial PGF2a secretion, to maintain luteal production of P4. IFNT binds to IFNARs on the endometrial luminal epithelium and superficial glandular epithelium to inhibit transcription of the *ESR1* gene through a signalling pathway involving IFN regulatory factor (IRF) 2. These antiluteolytic actions of IFNT on the *ESR1* gene prevent *ESR1* expression and, therefore, the ability of oestrogen to induce expression of OXTR required for pulsatile release of luteolytic PGF (Spencer *et al*., 2007).

There has been much interest in determining the differences in global transcriptome profiles in embryos derived following natural mating or artificial insemination compared to those produced using assisted reproductive technologies (ART), such as *in vitro* embryo production or cloning. It is now widely accepted that ART derived embryos have significantly altered gene expression patterns compared to their *in vivo* derived counterparts (Clemente *et al*., 2011; Gad *et al*., 2012) What is most striking, is that these embryos elicit diverging responses from their recipient maternal endometrium, even though IFNT production levels was found to be similar in these pregnancies (reviewed by Sandra *et al*., 2015), suggesting that other pathways than IFNT-mediated, are involved in recognition of pregnancy. Comparing endometrial transcriptomes of cows that were recipients of *in vivo*, IVF-derived or SCNT -embryos revealed distinct patterns of gene expression among the three groups (Bauersachs *et al*., 2009; Mansouri-Attia *et al*., 2009b). Moreover, studies show that the supply of numerous amino acids and derivatives was significantly lower in the endometrium of SCNT conceptus-carrying females (Groebner *et al*., 2011b; Dorniak *et al*., 2013a).

It is likely that the class I major histocompatibility complex (*MHC-I*) also plays a role in embryo maternal interaction and modulation of the maternal immune response. The *MHC*, termed the bovine leukocyte antigen (*BoLA*) in cattle and the human leukocyte antigen (Davies *et al*., 2006) in humans, encodes a collection of immune and non-immune related molecules (see Kelley *et al*., 2005, for review). The class I region of the *MHC* includes the classical, or class *Ia* genes, the non-classical (*NC*), class *Ib*, genes and a number of pseudogenes. Although not directly homologous, classical class I genes have common characteristics across all species, such as high levels of polymorphism and high expression levels; their main function is to discriminate between self and non-self by presenting antigenic peptides to cytotoxic T lymphocytes, thus eliciting an immune response. Non-classical class I genes are generally non-polymorphic, have lower expression levels and varied functions (Hughes *et al*.,1999; Ellis, 2004). Currently there are circa 90 full length class I cDNA sequences validated and listed in the bovine *MHC* database (http://www.ebi.ac.uk/ipd/ mhc/bola). There are six or more classical *BoLA* class I genes, expressed in a number of different combinations, such that no more than three are expressed on a haplotype (Ellis *et al*., 1999; Birch *et al*., 2008). The existence and genomic location on chromosome 23, of five bovine *MHC-Ib* genes (named *NC1-NC5*), is recorded on the database. Their expression has been demonstrated in early cleavage stage bovine embryos (Doyle *et al*., 2009) binucleate cells (Bainbridge *et al*., 2001) and in first and second trimester and term trophoblast tissues (Davies *et al*., 2006). In general, the classical class I genes are found to be down-regulated or modified in the trophoblast cell populations in many mammalian species (for review, see Ellis *et al*., 2004). *MHC-I* mRNA expression by bovine embryos is both transcript and embryo stage-specific (Doyle *et al*., 2009) and can be regulated by a number of cytokines including IFNG, IL-4, and LIF (O'Gorman *et al*., 2010; Al Naib *et al*., 2011). Humans express three classical class I genes (HLA-A, -B and -C), and a number of non-classical genes, including HLA-G. HLA-G is expressed by human trophoblast (Ellis *et al*., 1999), which exists in both membrane-bound and soluble (secreted) alternatively spliced forms. A literature survey on the role of soluble HLA-G (sHLA-G) reported that sHLA-G secreted by early embryos may be necessary for implantation and could represent a good non-invasive marker for pregnancy rate following IVF (Fuzzi *et al*., 2002; Rizzo *et al*., 2007). However, the association between sHLA-G concentration and implantation success is not robust (Tabiasco *et al*., 2009).

We have investigated the mRNA expression profiles of bovine embryos as different stages of pre and peri -implantation development. Embryos were recovered from slaughtered pregnant beef-cross heifers at days 16, 17, 20, 24 and 34 post AI. The relative abundance of trophectodermal *NC-MHC-I (BoLA- NC1, NC2, NC3 & NC4)* mRNA expression was analysed using quantitative real time PCR. mRNA expression of *NC BoLA* sequences was detected at all stages investigated, with expression increasing linearly with embryo development (Reddy *et al*., 2011). In human, successful trophoblast invasion appears to depend upon the appropriate combination of fetal HLA-C expression by trophoblast and killer cell immunoglobulin-like receptors (Rouas-Freiss *et al*., 1997) by maternal uterine natural killer (NK) cells, moreover, inappropriate combinations could lead to poor placentation as seen in pre-eclampsia (Hiby *et al*., 2004). It appears that extra-villous human fetal trophoblast cell HLA-G expression may also potentiate maternal immuno-tolerance through modulation of CD4+ T, CD8+ T and NK -cell activity (Rouas-Freiss *et al*., 1997; Bainbridge *et al*., 2000; Fournel *et al*., 2000; Mansouri-Attia *et al*., 2012; Tilburgs *et al*., 2015). In general, MHC class I or class I-like ligands bind to KIR and Ly-49 multigene family members. The KIRs are expressed by NK cells and subsets of T cells (Vilches and Parham, 2002); whereas leukocyte immunoglobulin-like receptors (LILR) are expressed by several types of leukocytes (Long, 1999). Binding of MHC-I ligands either inhibits or activates their effector functions. In cattle, inhibitory (KIR2DL or

KIR3DL) and activating (KIR2DS and KIR3DS) members have been identified (Storset *et al*., 2003). Non-classical BoLA are produced in both nonsoluble and soluble forms, so it has been speculated that the soluble BoLA also bind LILR receptors on leukocytes in cows, which could inhibit the leukocyte (Rapacz-Leonard *et al*., 2014). However, to date, their interaction with trophoblast MHC-I ligands has not been detailed.

Maternal immune cell response to pregnancy

Although studies on the involvement of the maternal immune system in the establishment of pregnancy in cattle are few in number, particularly, for early pregnancy, monocyte (Mo), macrophages MØ and dendritic cells (DCs) appear to be the key actors during the implantation period (Fair, 2015). Macrophage recruitment to the pregnant endometrium has been described for a wide range of mammalian species, including the mouse (Fest *et al*., 2007), human (Mincheva-Nilsson *et al*., 1994, McIntire *et al*., 2008), sheep and cattle (Tekin and Hansen, 2004; Oliveira and Hansen, 2009; Oliveira *et al*., 2010; Mansouri-Attia *et al*., 2012). Some of the roles associated with macrophages at this time include clearing cellular debris and regulating apoptosis (Straszewski-Chavez *et al*., 2005), and regulation of placental lactogen concentrations at the fetal–maternal interface (Kzhyshkowska *et al*., 2008). However, these roles may be more important for mouse and human, where implantation is quite invasive. An additional role, which may be more relevant to ruminant species, is regulating the activation of anti-conceptus immune responses (Oliveira *et al*., 2010) in response to IFNT stimulation and antigenicity of the conceptus due to paternal antigen and classical MHC protein expression (Doyle *et al*., 2009). In cattle, using immunofluorescent labeling of immune cell markers, we observed an initial expansion of Mo, MØs (CD14+-cells), and DC (CD172a–CD11c+) populations in the endometrial stroma on day 13 of pregnancy (Mansouri-Attia *et al*., 2012). At the same time there was a decline in the number of CD11b positive cells; the loss of CD11b expression is characteristic of monocytes acquiring a stationary phenotype (Mansouri-Attia *et al*., 2012). Which supports their accumulation in the endometrial stroma in response to the embryo. Similarly, a human and mouse -specific role of Dendritic cells is involvement in decidua formation (Blois *et al*., 2007; Plaks *et al*., 2008). Immunofluorescent labeling of CD172a and CD11c in bovine endometrium sections, revealed a large population of immature cells within the endometrial DC population during early pregnancy (Mansouri-Attia *et al*., 2012). Immature DC's have been associated with the initiation and maintenance of peripheral tolerance (Dietl *et al*., 2006) and their presence has been positively associated with the establishment of healthy pregnancies in women (Tirado-Gonzalez *et al*., 2010). The expansion of these populations in the maternal endometrium is likely to be induced by IFNT.

The maternal immune response to pregnancy in humans, has long been described as a Th1/Th2 dichotomy with an imbalance toward a Th2 type immune response (Wegmann, 1988; Raghupathy, 1997). However, with more in depth transcriptomic and proteomic profiling, this view has been expanded, to take in to account the reported endometrial expression of Th1-type cytokines during implantation and proposed associated requirements for inflammatory signaling during the establishment of pregnancy (Lin *et al*., 1993; Chaouat, 2007). Using fluorescent labeling of lymphocyte subset markers on endometrial sections, we identified CD4+, CD8+, gamma delta T and FoxP3+ lymphocyte populations in both pregnant and cyclic cattle from day 5 to 16 of pregnancy/oestrous cycle. The population sizes did not appear to be temporally regulated during the oestrous cycle, or by the presence of an embryo (Oliveira *et al*., 2013). Although the population size did not alter, the gene expression profile of these cells was temporally modified; inflammatory/Th1 immune factors *IFNA, LIF, IL1B, IL8,* and *IL12A* were down regulated during the luteal phase of the oestrus cycle, while Th2 factors *LIF* and *IL10* were upregulated. Our findings suggested that the inflammatory status of T-lymphocytes is modulated during the oestrous cycle, taken together with the similar transcriptome profiles of cyclic and pregnant endometrial tissue, it would appear that the default mechanism in the uterus is to prepare for, and expect, pregnancy (Forde *et al*., 2011). In contrast to our findings, Correia-Álvarez *et al*. (2015) reported reduced numbers of CD45-positive leukocytes in the endometrium three days after transfer of *in vitro* produced bovine day 8 blastocysts to the uterus of heifers, compared to those with sham transfers. Similarly, Groebner *et al*., 2011a reported fewer CD45-positive leukocytes in the zona basalis of pregnant animals on day 18 of pregnancy, simultaneous with an increase in transcripts and elevated enzymatic activity of the tryptophan (Trp) -degrading enzyme indoleamine 2, 3 dioxygenase 1 (IDO). The Authors proposed that the elevated enzyme activity resulted in local Trp ablation, which lead to the reduced the number of leucocytes in the zona basalis of pregnant animals on day 18. However, neither group identified the specific leukocyte subset that was regulated in their study. Endometrial TGFb2 expression is also down regulated during the ovine and bovine implantation period, but appears to increase specifically in the placentome at this time (Mansouri-Attia *et al*., 2012). Several roles have been proposed for TGFb2 during placentation: 1) chemoattractant for Mo recruitment to the placentation foci; 2) regulator of trophoblast invasion and 3) regulation of Mo inflammatory status (Wahl *et al*., 1987; Graham and Lala, 1991).

The final lymphocyte to address is the NK cell, which is an essential player in the establishment of pregnancy in mouse and human. Using immunofluorsecent labeling of CD335+ cells, we found these cells to be surprisingly elusive in bovine endometrial tissue, in cyclic animals and particularly during the early stages of pregnancy (Oliveira *et al*., 2013). There is evidence from an *vitro* study suggesting that uterine NK cell expansion could be restricted by

IFNT (Skopets *et al*., 1992). Given that in mouse and human, uterine NK cells are critically involved in local vascular remodeling and regulation of trophoblast invasion during implantation (Mor *et al*., 2011), the restricted NK expansion might be a contributory mechanism by which non-invasive implantation develops in cattle, see review by Bazer *et al*. (2009).

Peripheral response of the maternal immune system to early pregnancy

In addition to the local uterine immune response, extra-uterine tissues, including peripheral blood cells (PBL) and the corpus luteum, respond to conceptus secretions (Sandra *et al*., 2015). The systemic effect of the conceptus has also been investigated with regard to IFNT and the expression of ISG in peripheral blood leucocytes (PBL; Oliveira and Hansen, 2008) and (Ott and Gifford, 2010). As observed in the endometrium, gene expression of ISGs (*MX1, MX2, OAS1, ISG15*) is induced in bovine PBLs (Green *et al*., 2010; Pugliesi *et al*., 2014) by day 18. These suggest that PBL ISG expression could be evaluated to determine cow pregnancy status (Forde and Lonergan, 2012), or to characterize the post insemination PBL profile of cows that maintain their pregnancies or those that ultimately re-cycle.

Summary

The role of embryo derived IFNT and the importance of maternal macrophage and dendritic cells in the establishment of pregnancy in cattle is widely understood. Further support for basic research in the area of bovine reproductive immunology is essential to generate new knowledge of the mechanisms involved in maternal – embryo immunological cross-talk. This information will lead to a better understanding of the optimal maternal immunophenotype to support early embryo development and implantation and facilitate the optimization of transition and post-partum -cow management to ensure this phenotype is achieved prior to breeding.

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