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Maternal Immune Regulation by Conceptus During Early Pregnancy in the Bovine

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ABSTRACT

During early pregnancy in the bovine, it is necessary for the conceptus not only to block the luteal regression in order to ensure continual production of luteal progesterone but also to modify maternal immune system so as to prevent the fetus in uterus from the immune destruction. The present researches are concentrated on the immune regulation of maternal uterus, peripheral blood mononuclear leukocytes and corpus luteum which induced by interferon-tau, the primary pregnancy recognition signal in the bovine but it is not well understood for modulation of the maternal immune system by conceptus. In this review, we are not only concentrated on the advance in the immune regulation of maternal uterus and peripheral blood mononuclear leukocytes but also focus on the immune regulation by the secretions of conceptus beside interferon-tau. The secretions of conceptus beside interferon-tau include placental lactogen, pregnancy-associated proteins, prostaglandin E2, non classical MHC class I, GATA transcription factors, prolactin-related protein, Cox-2 and IL-6. Furthermore, interferon-tau may be involved in maternal systemic immune regulation through peripheral blood mononuclear leukocyte, platelets and cell-free DNA by the lymph circulation and blood circulation in the bovine.

Key words: Bovine, conceptus, immune regulation, interferon, pregnancy

INTRODUCTION

During early pregnancy in the bovine, the conceptus-derived signals must communicate to the maternal endometrium in order to maintain pregnancy. The survival for early embryo is involved in the regulation of maternal physiology, such as blocking the luteal regression so as to ensure continual production of luteal progesterone (P4) from the Corpus Luteum (CL). The main function of CL is to produce P4 which plays a key role in pregnancy establishment and maintenance. It is also essential for the bovine conceptus (embryo/fetus and associated membranes) to regulate maternal immune environment, so that, there is no maternal immune rejection against the conceptus and the mother, in her turn, must adjust her immune system to adapt the existence of conceptus (Hansen, 2011).

The fertilization rate is about 90% in cattle and an average calving rate is about 55%. The majority of embryonic loss (70-80%) occurs between day 8 and day 16 after insemination in cattle. However, the biological pathways and physiological processes which control maternal fertility is not

well understood in the bovine at present (Spencer, 2013). In this review, we are not only concentrated on the advance in the immune regulation of maternal uterus and peripheral blood mononuclear leukocytes but also focus on the immune regulation by the secretions of conceptus.

INTERFERON-TAU, THE PRIMARY CONCEPTUS SIGNALING IN THE BOVINE

Establishment of pregnancy begins at the blastocyst stage in the bovine and is involved in a two-way communication between the conceptus and the mother (Roberts *et al*., 2008). It is important that robust signaling from the conceptus must exert to the maternal uterus and the mother also needs to respond adequately to the conceptus signals. As the pregnancy recognition signal in cattle, interferon-tau (IFNT), is produced by the early conceptus, it interacts with the uterus and modifies the maternal environment.

INTRAUTERINE IMMUNE REGULATION BY IFNT

The conceptus inherits half of its genetic materials from the father but usually thrives within the maternal uterine environment without suffering any deleterious immune attack from the mother. Thus, the maternal intrauterine immune system must be modified so as to prevent the fetus in her uterus from the immune destruction. There is evidence that IFNT can lead to significantly increasing prostaglandin E2 (PGE2) synthesis and unaltered PGF2α production in cows (Guzeloglu *et al*., 2004).

The most significant variation in the total number and distribution pattern of the NK cell population were observed on 16th day of pregnancy in cattle and the mRNA transcript abundances of the immune factors including Leukemia Inhibitory Factor (LIF), Interleukin 1b (IL-1b), IL-10, IL-11 and IL-12A were temporally regulated during early pregnancy (Oliveira *et al*., 2013).

The intrauterine immune regulation by IFNT, in fact, is mostly through the janus kinase and signal transducers and activators of transcription (JAK-STAT) pathway which leads up-regulation of a range of Interferon Stimulated Genes (ISGs) in the endometrium at day 16-17 of pregnant cows comparing with cyclic dairy cows and down-regulated gene in pregnant cow is nitric oxide synthase 2 (NOS2) (Walker *et al*., 2010; Forde *et al*., 2011, 2012; Mamo *et al*., 2012) (Table 1).

Bone marrow stromal antigen 2 (BST2) induces the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activity in a dose-dependent manner in HEK293T, HeLa clone P4.R5 and HT1080 cells and NF-κB plays a key role in regulating the immune response (Tokarev *et al*., 2013). DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 (DDX58) gene encodes a protein containing RNA helicase-DEAD box protein motifs and a caspase recruitment domain (CARD) which is involved in the regulation of immune response in mice (Kolakofsky *et al*., 2012).

Eukaryotic translation initiation factor 4E (EIF4E) regulates the proliferation of T_{Foxp3-} and T_{Foxp3+} cells and affects Foxp3 expression in GFP-Foxp3 knock-in (ki) mice (Bjur *et al*., 2013). The Fc fragment of IgG, high affinity Ia, receptor (FCGR1A) can trigger autoimmune arthritis, thrombocytopenia, immune complex-induced airway inflammation, active and passive systemic anaphylaxis in mice (Mancardi *et al*., 2013).

HECT and RLD domain containing E3 ubiquitin protein ligase family member 6 (HERC6) knock-down can abolish global interferon stimulated gene 15 (ISG15) modification (ISGylation) in mouse cells and HerC6 is likely the functional counterpart of human HECT domain and RCC1-like domain containing protein 5 (HerC5) which mediates global ISGylation in human cells

Table 1: Cytokines related to intrauterine immune regulation

Cytokine	Abbreviation	Up or down
2'-5'-oligoadenylate synthetase 1	OAS1	Up
2'-5'-oligoadenylate synthetase 2	OAS2	Up
Bone marrow stromal antigen 2	BST2	Up
DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58	Up
Eukaryotic translation initiation factor 4E	EIF4E	Up
Fc fragment of IgG, high affinity Ia, receptor (CD64)	FCGR1A	Up
HECT and RLD domain containing E3 ubiquitin protein ligase family member 6	HERC6	Up
Interferon gamma-inducible protein 16	IFI16	Up
Interferon induced protein 35, Interferon induced protein 44	IFI35, IFI44	Up
Interferon induced protein 44 like	IFI44L	Up
Interferon induced with helicase C domain 1	IFIH1	Up
Interferon induced protein with tetratricopeptide repeats 1	IFIT1	Up
Interferon induced protein with tetratricopeptide repeats 2	IFIT2	Up
Interferon induced protein with tetratricopeptide repeats 3	IFIT3	Up
Interferon induced protein with tetratricopeptide repeats 5	IFIT5	Up
Interferon induced transmembrane protein 1	IFITM1	Up
Interferon induced transmembrane protein 3	IFITM3	Up
Interferon induced transmembrane protein 5	IFITM5	Up
Interferon responsive gene 15	IFRG15	Up
Interferon regulatory factor 1, Interferon regulatory factor 3	IRF1, IRF3	Up
Interferon regulatory factor 5, Interferon regulatory factor 6	IRF5, IRF6	Up
Interferon regulatory factor 8	IRF8	Up
Interferon stimulated gene 15, Interferon stimulated gene 20	ISG15, ISG20	Up
Myxovirus resistance 1, Myxovirus resistance 2	MX1, MX2	Up
Potassium large conductance calcium-activated channel, subfamily M, alpha member 1 subfamily M, alpha member 1	KCNMA1	Up
Proteasome subunit beta type 8, Proteasome subunit beta type 9	PSMB8, PSMB9	Up
Radical S-adenosyl methionine domain containing 2	RSAD2	Up
Suppressor of cytokine signaling 1	SOCS1	Up
Signal transducers and activators of transcription 1	STAT1	Up
Signal transducers and activators of transcription 2	STAT2	Up
Sterile alpha motif domain containing 9	SAMD9	Up
Transporter 1, ATP-binding cassette, sub-family B	TAP1	Up
Transporter 2, ATP-binding cassette, sub-family B	TAP2	Up
Ubiquitin-like modifier-activating enzyme 7	UBA7	Up
Ubiquitin specific peptidase 18	USP18	Up
Nitric oxide synthase 2	NOS2	Down

(Oudshoorn *et al*., 2012). HERC6 may be implicated in intrauterine immune suppression through regulation of ISG15 conjugation in cows. Ubiquitin-like modifier-activating enzyme 7 (UBA7) is also known as the ISG15-conjugating enzyme UbE1L which is involved in immune response through activating ISG15.

It was reported that interferon induced transmembrane protein 1 (IFITM1) could act as an immune inhibitive molecule through suppressing NK cells in gastric cancer cells (Yang *et al*., 2005). Up-regulation of interferon induced protein with tetratricopeptide repeats 1 (IFIT1), IFIT4, 2'-5'-oligoadenylate synthetase 1 (OAS1), OAS2 and OASL in human peripheral white blood cells

was related to the autoimmune disease which indicated that these ISGs were involved in immune suppression (Ye *et al*., 2003). As an intracellular DNA sensor, IFI16 mediates the induction of interferon-β in human peripheral blood mononuclear cells which is critical for appropriate innate immune responses (Unterholzner *et al*., 2010).

As an ubiquitin-like protein, ISG15 can bind covalently its target proteins to regulate their function and also regulate maternal intrauterine immunosuppressive through ISG15 modification (Yang *et al*., 2010a). Interferon stimulated exonuclease gene 20 kDa (ISG20) is a 3'-5' exonuclease with a preference for single stranded RNA over single stranded DNA and is a major effector of innate immune response against various pathogens (Degols *et al*., 2007). Interferon Regulatory Factor 1 (IRF1) plays a critical role in inducible expression of MHC class I in cells from IRF-1 deficient mice and the IRF-8/IRF-1 complex can induce expression of numerous genes which are important for macrophage differentiation and macrophage-induced inflammation (Paun and Pitha, 2007).

The proteasome (prosome, macropain) subunit beta type 8 (PSMB8) and PSMB9 are also named as Low Molecular Weight Proteosome (LMP7) and LMP2. The LMP2 gene was required for the expression of Human Leukocyte Antigen (HLA) class I molecules in human hepatocellular carcinoma cell line. The LMP7 was not the major reason for loss of HLA class I in human hepatocellular carcinoma cell line, although, the supply of exogenous LMP7 could increase surface expression of HLA class I antigen (Shen *et al*., 2007). Potassium, large conductance calcium-activated channel, subfamily M, alpha member 1, (KCNMA1) was involved in the cross-talk between immune and cardiovascular systems through human β-defensin 2 in monkeys (Liu *et al*., 2013a).

Radical S-adenosyl methionine domain containing 2 (RSAD2) is also known as virus inhibitory protein (Viperin) which plays a role in $CD4^+$ T-cells activation and differentiation. The RSAD2 can facilitate T Cell Receptor (TCR) which mediates GATA-3 activation and production of optimal Th2 cytokine by modulating NF-kappaB and AP-1 activities in mice (Qiu *et al*., 2009). Sterile Alpha Motif Domain 9 (SAMD9) regulates cell proliferation and apoptosis and decreases tumor growth of colon cancer cell line in immune deficient mice (Li *et al*., 2007).

Suppressor Of Cytokine Signaling 1 (SOCS1) proteins are inhibitors of the cytokine signaling pathways and are key physiological regulators of both innate and adaptive immunity and the expression of SOCS3 by SOCS3-deficient DCs plays a crucial role in the balance between Th2 cells and regulatory T cells (Yoshimura *et al*., 2007). It is demonstrated that STAT2 is functionally involved in the immunosuppressive activity of human clonal mesenchymal stem cells (Yi *et al*., 2012). Kalkunte *et al*. (2009) reported that it was through induction of the Transporter 1, ATP-binding cassette, sub-family B (TAP1) protein that vascular endothelial growth factor-C protected endothelial and trophoblast cells from human uterine NK cells.

Ubiquitin Specific Peptidase 18 (USP18) is important in regulating the type I interferon signaling in innate immunity and also can regulate T cell activation and T helper 17 (Th17) cell differentiation in USP18-deficient mice (Liu *et al*., 2013b). As a free radical, NO is synthesized by conversion of l-arginine to l-citrulline catalyzed through Nitric Oxide Synthase (NOS) which promotes immune cell activation and apoptosis in SelK KO mice (Huang *et al*., 2012). The IFNT may be regulate the above cytokines that are involved in immune regulation in human or mice which may provide a local immune regulation to facilitate the survival of embryo within the uterus in the bovine.

EFFECT OF IFNT ON OTHER TISSUES BESIDE UTERUS FOR IMMUNE REGULATION

The ISGs, such as ISG15, OAS-1, IRF1, Mx1 and Mx2, PARP12, SAMD9 and HERC6 are also induced by IFNT in blood cells and CL in cows (Gifford *et al*., 2007; Yang *et al*., 2010b; Forde *et al*., 2012; Kizaki *et al*., 2013). It is reported that there are significant differences between the pregnant and nonpregnant cows in the circulating, cell-free DNA profile in sera during early gestation (Mayer *et al*., 2013).

It is reported that ISGs and IL-10 are expressed in Peripheral Blood Immune Cells (PBIC) including peripheral blood immune cells, Peripheral Blood Mononuclear Leukocytes (PBMCs) and polymorphonuclear granulocytes (PMNs) which is responsive to IFNT before the Maternal Recognition Period (MRP) in cattle (Shirasuna *et al*., 2012a). It is presumed that IFNT is involved in the systemic immune regulation through inducing the expression of ISGs and IL-10 in PBIC.

It is reported that infusion of exogenous IFNT into the uterine lumen via indwelling catheters or systemically by subcutaneous or intramuscular injections could extend CL lifespan in non-pregnant cows. We also reported that up-regulation expression of ISG15 in the bovine CL is due to high-level IFNT expression by conceptus during early pregnancy which is not through an endocrine mechanism in cows (Yang *et al*., 2010b).

The lymphatic system is the second circulation system and is necessary for immune function. It is IFNT from the conceptus in uterus that activates luteal lymphangiogenesis during MRP which results in the restitution of lymphatic system in the bovine CL (Nitta *et al*., 2011). Both endocrine system and circulating immune cells can transmit the information of developing embryo in uterus to ovary and the bovine luteal development, maintenance and regression are critically regulated by the specific immune cells, including macrophages, eosinophils and neutrophils. It is the lymphatic system but not the blood vascular system, that is reconstituted in the bovine CL which is induced by IFNT from conceptus during early pregnancy (Shirasuna *et al*., 2012b).

It is the ISGs such as ISG15, OAS-1, IRF1, Mx1 and Mx2 that are expressed by PBIC and CL induced by IFNT from conceptus which implies that PBIC may be involved in regulating systemic immune response. These changes in PBICs may be part of the process by which pregnancy is facilitated (Hansen, 2011). It is not only PBMC but also circulating platelets that are possible sources of chemokines which are implicated in embryo-maternal cross-talk in human (Fujiwara, 2009).

We reported that ISG15 conjugated proteins are expressed in a tissue specific manner induced by IFNT which exerts different effects on different tissue (Yang *et al*., 2012). The IFNT from conceptus exerts different effects, such as anti-luteolysis effect in CL and modification of maternal immune response in immune organ through stimulating different expression pattern of ISG15 conjugated proteins in different tissue or organ. We also found that the IFNT from conceptus had an obvious effect on bone marrow and thymus. Therefore, it was presumed that IFNT may be involved in regulating innate immune response in different tissues or organ through lymph circulation, blood circulation and endocrine system during early pregnancy in the bovine. In the lymph circulation and blood circulation, it may be P4, PBMC, platelets and cell-free DNA in sera which were involved in regulating innate immune response during early pregnancy in the bovine (Fig. 1).

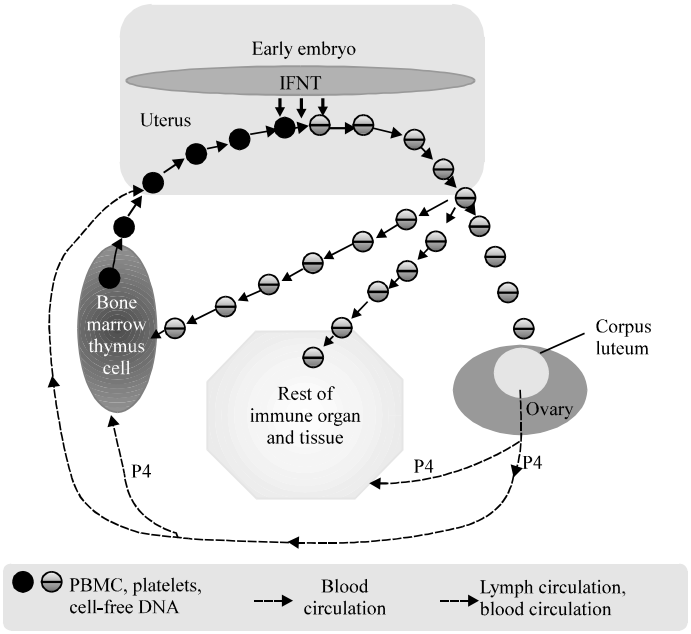

Fig. 1: Mechanism of modulating the maternal immune response systemically by the conceptus during early pregnancy in the bovine. The Peripheral Blood Mononuclear Cells (PBMC), platelets and cell-free DNA from bone marrow, thymus and cells are not modulated by hormones and cytokines. Firstly, they enter blood circulation, are modulated by high level of P4 from corpus luteum during early pregnancy. And then, the PBMC, platelets and cell-free DNA migrate through blood circulation to endometria, are meanwhile modified directly or indirectly by interferon tau (IFNT) and other active materials from the conceptus. The functional changed PBMC, platelets and cell-free DNA carry some specific information on the presence of the conceptus. The information carried by the PBMC, platelets, cell-free DNA is amplified and transmitted to effector cells through lymph circulation and blood circulation to affect the function of the immune organs and non-immune organs including ovary

UTERINE IMMUNE REGULATION BY THE SECRETIONS OF CONCEPTUS BESIDE IFNT

At the time of conceptus elongation, immune suppression is reinforced by the secretions from conceptus. In addition to IFNT, other secretions from conceptus are also involved in regulating maternal immune responses. Other products that are produced by the conceptus include Placental Lactogens (PLs), Pregnancy-Associated Glycoproteins (PAG), PGE2, non-classical MHC class I, GATA transcription factors, Prolactin-Related Protein (PRP), Cox-2 and IL-6. In addition, there is a down-regulation of MHC class I by early embryo in the bovine (Fig. 2).

Placental lactogen, also known as Human Chorionic Somatomammotropin (HCS) in human, is secreted by binucleate cells of trophoderm and releases into both the maternal and fetal circulation. The PL could be detected in trophoblastic tissue as early as day 17 of pregnancy in cows. The level of maternal concentration of PL is higher than that in the fetus circulation in cattle, however, it does not happen in other species. The HCS is supposed to inhibit the T lymphocyte proliferation in human by trophoblast culture or villous explant culture through thymidine incorporation analysis (Dong *et al*., 2008).

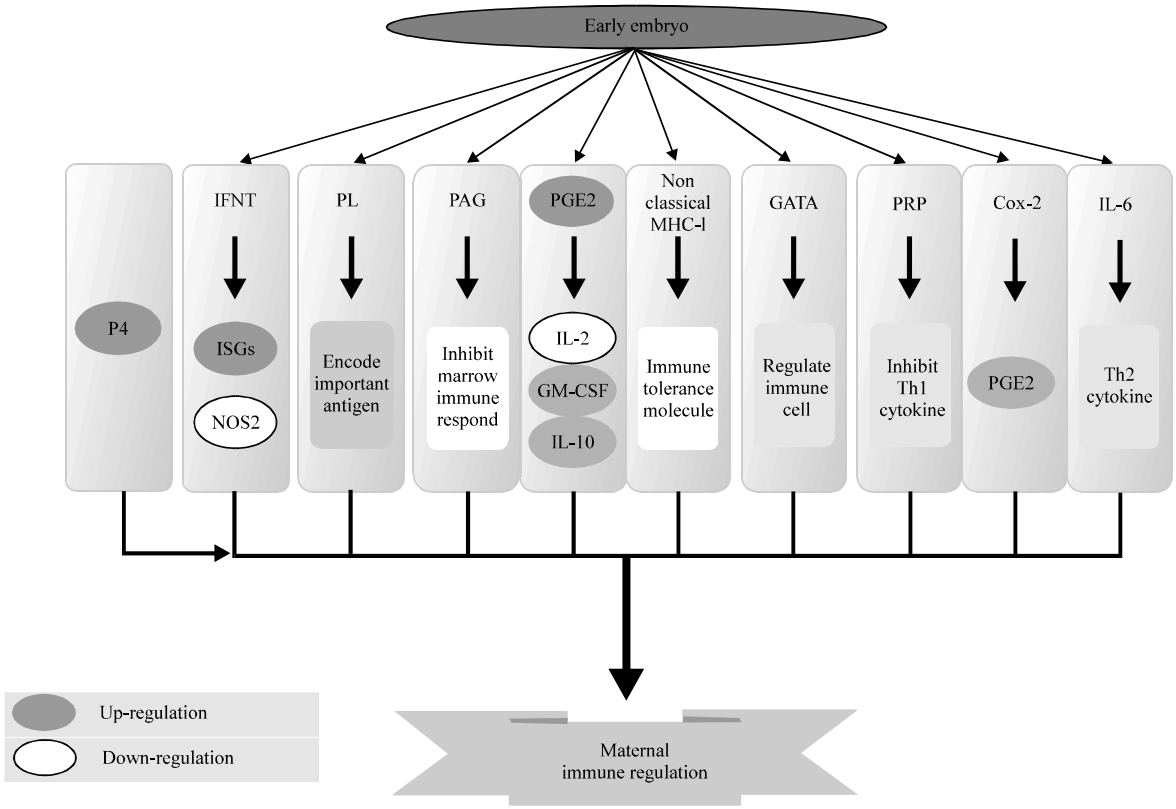

Fig. 2: Maternal immune regulation by secretions from the conceptus and progesterone. During early pregnancy in the bovine, maternal immune regulation is reinforced by secretions from the conceptus, including interferon tau (IFNT), Placental Lactogen (PL), Pregnancy-Associated Glycoprotein (PAG), prostaglandin E2 (PGE2), non-classical MHC class I, GATA transcription factors, Prolactin-Related Protein (PRP), cyclooxygenase-2 (Cox-2) and interleukin 6 (IL-6). Meanwhile progesterone (P4) from corpus luteum is also involved in maternal immune regulation. ISGs, interferon stimulated genes, NOS2, nitric oxide synthase 2, GM-CSF, granulocyte-macrophage colony-stimulating factor

The PAG is one of the major trophoblast secretory products in cattle. The expression of PAG occurs throughout the trophectoderm and the PAG is predominantly localized to binucleate cells. The expression of PAG varies in a temporal manner during pregnancy and boPAG-4, -5 and -9 are expressed in earlier stages of pregnancy. It was reported that PAG inhibited the proliferation of bone marrow progenitor cells *in vitro* in dairy cows (Dosogne *et al*., 2000).

Prostaglandins (PGs) are secreted by day 13 conceptus in the bovine and act locally in a paracrine manner to alter gene expression in the endometrium (Spencer *et al*., 2013). It was reported that PGE2 could inhibit proliferation of lymphocytes in a concentration-dependent manner. The PGE2 also acts as a potent pro-inflammatory mediator through inducing IL-8 gene transcription in activated T lymphocytes. MacKenzie *et al*. (2013) also reported that PGE2 could induce high expression of macrophage IL-10 production in mice. The IL-10 is a pleiotropic molecule which displays both immunostimulatory and immunoregulatory activities.

Al Naib *et al*. (2011) reported that the expressions of non-classical MHC class I genes, including NC2, NC3 and N4, were modified in a gene and cytokine-specific manner in the *in vitro* bovine

embryos and the successful pregnancy was related to up-regulation of non-classical MHC class I. Non-classical MHC class I protects target cells from NK-cell and cytotoxic T lymphocytes mediated lyses and is also associated with loss of MHC class I expression in human.

GATA transcription factors are a family of transcription factors characterized by their ability to bind to the DNA sequence "GATA". It was reported that GATA2 and GATA3 were expressed in the bovine trophoblast cells during peri-attachment period and were regulated by trophoblast factors including IFNT, decreased in the conceptus after attachment to the uterine epithelium (Bai *et al*., 2011). The GATA1 is a transcriptional regulator of dendritic cell differentiation and dendritic cells are key initiators and regulators of the immune response in mice (Gutierrez *et al*., 2007).

Both bovine PRP-I mRNA and protein appeared in trophoblastic binucleate cells and multinuclear cells first at day 20 of pregnancy in cows (Yamada *et al*., 2002). Prolactin receptors (PRL-R) are situated on surface of the immune cells, including T-lymphocytes, B-cells and macrophages. Low concentration of PRL induces the production of Th1 type cytokines in T-cells *in vitro* but high concentration of PRL causes inhibition of the production of Th1 type cytokines.

Cyclooxygenase is officially known as prostaglandin endoperoxide synthase (PTGS). High expression of Cox-2 from blastocyst results in successful pregnancy (El-Sayed *et al*., 2006). Cox-2, as a prostaglandin endoperoxide synthase, is responsible for the conversion of arachidonic acid into prostaglandin H2 which is the common precursor of PGE2. Therefore, Cox-2 may be involved in modulation of maternal immune function through promoting synthesis of PGE2.

T cells and macrophages secrete IL-6 to stimulate immune response. Mathialagan *et al*. (1992) reported that IL-6 mRNA was expressed in elongating preimplantation conceptus in cows. IL-6 is mainly produced by Th2 cells that may be involved in recognition of pregnancy and immune tolerance which is necessary for successful pregnancy. In cows, transcript abundance of MHC class I gene declines after blastocyst hatching (Doyle *et al*., 2009). The low level expression of MHC class I may ensure that a tissue rejection response against the embryo is not invoked because MHC class I is involved in the activation of NK cell responses (Hansen, 2011).

CONCLUSION

As a foetal allograft to the mother, the conceptus must produce hormones and cytokines which regulate the maternal intrauterine immune and systemic immune response. During early pregnancy in the bovine, IFNT not only blocks the luteal regression but also regulates maternal immune response. IFNT induces expression of a range of ISGs in the endometrium which is involved in the regulation of maternal intrauterine immune. Meanwhile, the conceptus produces other active materials besides IFNT, including PLs, PAGs, PGE2, non-classical MHC class I, GATA transcription factors, PRP, Cox-2 and IL-6 which are also implicated in the regulation of maternal immune response in cows (Fig. 2). In the lymph circulation and blood circulation, IFNT may be involved in the maternal systemic immune regulation through PBMC, platelets and cell-free DNA in sera (Fig. 1).

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