Indoleamine 2, 3-dioxygenase (IDO) mediated Th1-Th2 shift, modulates the maternal immune system and decipher pregnancy outcomes in dairy cattle

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Abstract:

Background

In the current scenario, a decrease in the production potential of dairy cattle particularly due to the reduced reproductive efficiency is a major concern for the farmers and field veterinarians. Therefore, enhancement of reproductive efficiency is the need of the hour to raise the production potential of dairy cattle. Reproductive failure in terms of infertility, subfertility and dreadful embryonic mortality are some of the major substantial factors responsible for lowering the reproductive efficiency in dairy cattle. Such serious issues can be tackled and minimized by expanding the knowledge in the field of bovine pregnancy and unravel different mechanisms of pregnancy establishment in bovines. This will enable and motivate researchers to discover some possible and suitable interventions around these mechanisms in order to increase the pregnancy outcomes in dairy cattle. Although, there are many mechanisms which have been delineated so far for the pregnancy establishment in bovine but still many areas remain untapped which needs to be taken into limelight. Exploring different mechanisms in early bovine pregnancy may help to improve the reproductive efficiency in bovines and thereby production potential in the dairy sector.

Major advances

This chapter provides an insight into different immune tolerance mechanisms associated with the implantation of the blastocyst and early pregnancy establishment in bovines. During the early

pregnancy period (where a majority of embryonic loss occurs), it is imperative for the conceptus not only to prevent the corpus luteal regression but also to modify the maternal immune system from immune rejection. In this regard, interferon tau (IFNτ), a conceptus secreted factor, known to have anti-luteolytic and immunomodulatory properties and is the key pregnancy recognition agent in bovines, plays a preliminary and vital role in the establishment of bovine pregnancy. Whether it is by paracrine or by endocrine manner, IFNτ modulates the maternal immune system and helps in the establishment of pregnancy. Besides IFNτ, another crucial molecule recently came into limelight is indoleamine 2, 3-dioxygenase (IDO), which is an interferon-induced tryptophan catabolic enzyme and is the first and rate-limiting enzyme of the tryptophan catabolism via the kynurenine pathway. It is known to modify the maternal immune system by altering the T cell metabolism and thereby inhibiting the allo-reactive T cell proliferation and at the same time promoting the proliferation of immunosuppressive T regulatory cells. Moreover, to achieve successful implantation, IDO favors an anti-inflammatory cytokine milieu by inducing a shift towards the Th2 cytokines. Although many mechanisms have been delineated so far for the pregnancy establishment in bovine, the focus of this chapter resides on the role of IFNτ and IDO associated Th1-Th2 shift for a successful pregnancy with major emphasis on the tolerogenic mechanism of these molecules.

Keywords: Bovine, Pregnancy, IFNτ, IDO, Th1-Th2 shift.

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Abbreviations:

3-HAA: 3-hydroxyanthranilic acid

AhR: Aryl hydrocarbon receptor

AI: Artificial insemination

BoLA-1: Bovine leukocyte antigen-1

CL: Corpus luteum

GCN2: General control non-repressed 2

IDO: Indoleamine 2, 3-dioxygenase

IFNγ: Interferon gamma

IFNτ: Interferon tau

ISGs: Interferon stimulating genes

MHC: Major histocompatibility complex

MRP: Maternal recognition of pregnancy

PBL: Peripheral blood leucocytes

PBMC: Peripheral blood mononuclear cells

PDK1: Phosphoinositide-dependent kinase-1

VEGF: Vascular endothelial growth factor

Introduction:

Reproduction is an essential, yet critical phenomenon adopted by every species to propagate from one generation to another. A successful reproduction comprises many imperative factors out of which, proper gamete formation, timely gamete transfer & fertilization, maternal recognition of pregnancy (MRP) and implantation of the semi-allogeneic fetus into the mother's uterus are considered to be the most important factors for achieving success in pregnancy. In bovines, as production is directly related to its reproduction, therefore, optimal reproductive efficiency is of utmost importance so as to increase their production competency. In order to achieve maximum reproductive efficiency, proper detection of heat, timely insemination and identification of animals returning to heat post-artificial insemination (post-AI) is indispensable. Moreover, successful establishment of pregnancy also plays a crucial factor in bovine reproduction, as failure in this process leads to poor productivity of the animals (Koot et al., 2012; Norwitz et al., 2001). However, the perspective of pregnancy establishment switched into a different angle, when immunologists intervened and hypothesized a new dimensional role of various undiscovered agents such as enzymes, nucleic acid (fetal DNA) and several maternal immune cells in achieving successful pregnancy establishment in bovines. This new approach of understanding pregnancy has not only changed the traditional concept of hormonal role in pregnancy establishment (Spencer and Bazer, 2004) but has also helped immunologist to

manipulate maternal immune cells at different stages of pregnancy to enhance the reproductive efficiency. Various maternal immune cells play a balanced and orchestrated role in pregnancy establishment and allow the allograft fetus to acquire a suitable niche in the maternal endometrium without undergoing rejection (Than et al., 2019; Robillard et al., 2022). Besides the cellular role, the impact of different humoral factors like cytokines is inevitable. In association with different immune cells, these humoral factors play a paramount role in the successful establishment of pregnancy. Controlled activation of the maternal immune response during pregnancy is yet another vital process that renders simultaneous responsiveness towards unforeseen infections and at the same time provides tolerance towards the paternal antigen and semi-allogeneic fetus for a successful pregnancy (Mor and Cardenas, 2010). Understanding the mechanisms involved in the process of implantation and early pregnancy establishment may significantly improve the reproductive efficiency and thus productivity in the animal sector. During the past decades, changes in the morphology and histology of endometrium and molecular mechanisms behind the feto-maternal crosstalk during the implantation window have been intensively documented in mouse and humans (Zenclussen and Hämmerling, 2015; Meyer and Zenclussen, 2020; Das et al., 2021). However, limited literature is available explaining the inter-relationship between the Th1-Th2 cytokine shift and immune tolerance mechanism by indoleamine 2, 3-dioxygenase (IDO) during the implantation window in bovines. Hence, this chapter provides an overview of these processes and discusses the immune tolerance mechanisms associated with the implantation of the blastocyst and early pregnancy establishment in bovines.

Key elements of early pregnancy establishment:

Existing works of literature in the public domain provides a plethora of information and hypothesis related to early pregnancy establishment in bovines (Oliveira et al., 2012; Pohler et al., 2020); however, this chapter focuses on three crucial aspects of early pregnancy establishment viz. maternal recognition of pregnancy (MRP), Th1-Th2 cytokine shift and immune tolerance mechanism by IDO. Each element has been discussed in detail with the main focus on the immune tolerance mechanism of IDO behind the embryo survivability during early pregnancy establishment in bovines.

1. Maternal recognition of pregnancy (MRP) in bovines:

Priming of the maternal immune system:

The foundation of every successful pregnancy depends upon the bidirectional communication between the embryo and the mother and this process starts much before the embryonic tissue becomes intimately attached to the uterine epithelium. Dekker and Robillard, 2007 reported that maternal tolerance towards the paternal antigen is initiated much before the actual conception. A study conducted in mice model suggests that the seminal plasma secreted by the accessory glands i.e. seminal vesicles and prostate gland of the male reproductive system contains various signaling agents including estrogen, testosterone, transforming growth factor β (TGF-β), prostaglandins and glycoproteins (Maegawa et al., 2002) which interact with the epithelial cells of cervix and uterus causing modulation of the maternal immune system (Moldenhauer et al., 2009; Robertson et al., 2009). The role of seminal plasma in modulating different cellular and molecular adjustments of the maternal reproductive environment for a successful pregnancy in different domestic species has been extensively reviewed by Bromfield, 2016. Moreover, a recent study in cattle demonstrates that seminal plasma exposure to the female reproductive tract through natural mating affects conceptus development (Mateo-otero et al., 2020). This type of modulation of the maternal immune system occurs as a consequence of the effect of these seminal factors and the process is known as the "priming of the maternal immune system". This process renders endometrial tissue remodeling and cause improvement in its receptivity towards the implanting embryo (Robertson, 2005). Therefore, priming of the maternal immune system is considered as pivotal preliminary step, absolutely necessary before the actual process of implantation and pregnancy establishment.

Process of maternal recognition of pregnancy (MRP)

After establishment of the priming of the maternal immune system, the next critical stage is the attachment of embryo into the mother's uterus (implantation). Prior to implantation, the developing embryo gives early pregnancy signal which is recognized by the maternal endometrium and immune cells that allows the growing conceptus for implantation. This process is known as maternal recognition of pregnancy (MRP). MRP is a physiological phenomenon in which the embryo gives a signal to the mother about its whereabouts. It renders the abrogation of

the luteolytic mechanism and allows corpus luteum (CL) for the continuous production of progesterone throughout the gestation cycle. There are different endocrine mechanisms involved in different species that recognizes the presence of pre-attachment embryos, including the two best-known endocrine mechanisms comprised of estrogens produced by the porcine trophoblast (Perry et al., 1973) or interferon tau (IFNτ) produced by early conceptus in ruminants (Bazer et al., 1991; Spencer and Bazer, 2004) (Table-1). The duration of the pre-implantation period also varies among different species, for instance, in case of ewes the elongating conceptus adheres to the uterine epithelial surface and placentation starts around day 19 of gestation (Guillomot et al., 1981; Boshier, 1969), in cattle placentation is around day 22 (Guillomot and Guay, 1982), whereas, in mares the implantation is delayed until around day 37 of gestation (Allen et al., 1973). Whatsoever may be the agents of MRP in different species, without the involvement of these fundamental molecules, it is impracticable to protect the semi-allogeneic fetus from maternal immune rejection.

Interferon tau (IFNτ), the key MRP agent in bovines:

It is the IFNτ in ruminants which helps the conceptus to get implanted into the mother's uterus without undergoing rejection. IFNτ is a type-I interferon made up of single chains of amino acids unique to the ruminants. It is believed that 36 million years ago IFNτ was evolved from interferon omega (IFNω) by some rearrangement and/or insertion events that combined IFNω gene with the trophoblast specific promoter/enhancer (Ealy and Wooldridge, 2017). IFNτ is secreted from the mononuclear trophoblast cells of a viable conceptus and possesses antiviral, antiproliferative and immunomodulatory properties (Michael Roberts, 1989a). In bovines, the secretion of IFNτ starts from day 8 and goes up to 21-25 days post fertilization after which its synthesis ceases. The peak level is around 14-18 days post fertilization (Martal et al., 1979). The concentration of IFNτ and the size of the embryo are directly proportional to each other and report suggests that there is an increase in IFNτ concentration with the increase in embryo size during elongation (Robinson et al., 2006).

The question regarding molecular mechanism behind MRP still remains elusive.? There are many schools of thought which explains the role of IFNτ in MRP, but the common ground to the various thoughts is that the episodic release of prostaglandin PGF2α from the endometrium is regulated by the hormone oxytocin which is mediated via the coupling of oxytocin with its

receptor. IFNτ acts locally in a paracrine manner and inhibits the expression of the estrogen receptor which in turn abate oxytocin receptor expression in endometrium. Due to this phenomenon, endometrium fails to produce the luteolytic agent PGF2α, thus preventing lysis of corpus luteum and there is a continuous production of progesterone (Spencer et al., 1995). Apart from inhibiting luteolysis, IFNτ has also an impact on different intra and extra-uterine tissues in bovine (Oliveira et al., 2008). Through a paracrine manner, IFNτ acts on the endometrial tissue and induces several genes that directly or indirectly assist conceptus elongation and implantation (Bazer et al., 2008). These induced genes are broadly called as interferon stimulating genes (ISGs) which can also be induced by other type I interferons (Hansen et al., 2010; Pervolaraki et al., 2018). Although IFNτ locally alters the expression of more than 750 ISGs in the endometrium, some ISGs like interferon-stimulated gene 15 (ISG15), 2'-5'-oligoadenylate synthetase 1 (OAS1) and myxovirus resistance (MX1 and MX2) showed higher and differential expressions during early day 16 post-AI (Forde et al., 2011) and hypothesized to be used as early pregnancy diagnosis markers. Besides stimulating the intrauterine tissues, IFNτ has also a significant impact on extra uterine tissues (Endriß et al., 2021; Sheikh et al., 2018). An undetectable level of IFNτ when enters local or peripheral circulation from the uterus causes significant molecular changes in extra uterine tissues like CL (Shirasuna et al., 2015), peripheral blood leucocytes (PBL) (Gifford et al., 2007), peripheral blood mononuclear cells (PBMCs) (Matsuyama et al., 2012), neutrophils (Panda et al., 2020) and hepatocytes (Ruhmann et al., 2017) through endocrine manner. It is now well known that, in order to carry out pregnancy establishment under the expenses of a foreign fetus, IFNτ inhibits lymphocytes proliferation and induces neutrophil chemotaxis toward uterus to start a non-specific immune response in the uterus (Teixeira et al., 1997). Also, there are other reports which suggest a decrease in the neutrophil activity during the peri-implantation period and are believed to be attributed towards the IFNτ stimulation (Mohammed et al., 2017b). Moreover, IFNτ increases the expression of bovine leukocyte antigen-1 (BoLA-1) in bovine endometrial luminal epithelial cells which is known to have profound immunosuppressive effects during early embryonic development in bovines. BoLA-1 inhibits the proliferation of cytotoxic T cell and natural killer cell (NK cell) which ultimately induces feto-maternal tolerance in bovines (Zhu et al., 2017). According to them, IFNτ up-regulates the expression of anti-inflammatory cytokine IL-10 while decreases the expression of pro-inflammatory cytokine IL-6 in the endometrial tissue of bovines. After

unravelling so many different roles of IFNτ in bovine pregnancy, it is interesting to take a note that this 24 kDa molecule has numerous potential and pivotal functions which renders the process of pregnancy towards its success.

2. Th1-Th2 cytokine balance during pregnancy:

Pregnancy exhibits an immunological paradox state which is the most unique and challenging task for the maternal immune system. A successful pregnancy requires significant modulation of the maternal immune system that facilitates the acceptance of specific foreign antigens to support reproductive function without compromising maternal immune protection from pathogenic infections and inflammatory insults. Under such an immunological contradiction state, an increase in innate immune activity may be expected to protect the uterus from infection. But, this precise regulation of maternal immune modulation remains somewhat elusive. Several mechanisms have been proposed by different scientists that render the embryo to survive in the maternal environment. One of them includes the antigenic immaturity of the conceptus during which the bovine trophoblast, like other mammalian species, doesn't express classical polymorphic major histocompatibility complex (MHC) class 1 proteins in areas in touch with the maternal endometrium during early pregnancy (Bainbridge, 2000) which gives maternal immunological dormancy to the conceptus or localized immune tolerance to the growing conceptus (Medawar, 1953). Besides priming of the maternal immune system, early embryonic signal i.e. MRP and antigenic immaturity of the conceptus, a delicate harmony between pro and anti-inflammatory cytokines is also needed for successful establishment and maintenance of pregnancy.

Classification of Th1 and Th2 cytokines:

Cytokines are the soluble hormone-like proteins which are secreted by white blood cells as well as many other cells like endothelial cells, epithelial cells, and fibroblast. Cytokines include chemokines, monokines, lymphokines, interleukins, colony-stimulating factors, tumor necrosis factors, interferons, etc. They mediate several functions like inflammation, immunity by influencing cellular recruitment, proliferation, differentiation, activation, migration, suppression and killing. T-lymphocytes are considered as the major source of cytokine production and their cytokine secretion profile largely depends upon the availability of cytokines in their

microenvironment which helps the naive T helper (Th0) cells to mature and differentiate into different subtypes. When Th0 cells are exposed to IFNγ they become Th1 cells and if they are exposed to IL-4 they differentiate into Th2 type cells (Palmer and Van Seventer, 1997; Asnagli and Murphy, 2001). The cytokines produced by these two subsets are respectively known as Th1 and Th2 cytokines. Th1 cytokines are regarded as the pro-inflammatory cytokines which are responsible for inflammatory response whereas, Th2 cytokines are known as anti-inflammatory cytokines responsible for downregulation (suppression) of exaggerated and/or inappropriate Th1 response (Gianfranco Del Prete, 1998; Panda et al., 2020; Mohapatra et al., 2020). The major Th1 cytokine is IFNγ which is regarded as the most potent inflammatory agent. Besides IFNγ, other cytokines like TNFα, IL-2, IL-8, IL-12 and IL-17 are also considered as potent inflammatory agents, grouped under Th1 cytokines. In contrast, Th2 responses are characterized by the production of various Th2 cytokines like IL-4, IL-5, IL-10 and IL-13 which are associated with anti-inflammatory response (Garra, 2000; Kurt, 1987; Romagnani, 1992). Other T-helper responses include T-regulatory (T-reg) cell responses, determined by the secretion of IL-10 and TGF-β, and Th17 responses, defined by the secretion of IL-17 (Mucida, 2010).

Potent bovine pregnancy-associated cytokines (Th1 and Th2)

IL-1 family comprises 11 cytokines out of which IL-1α and IL-1β are the most studied ones and are known to have pro-inflammatory nature. According to Oliveira et al. 2013, the presence of embryo in the pregnant bovine endometrium lowered the mRNA expression of IL-1 β when compared to the cyclic cows. Additionally, non-pregnant cows exhibited higher plasma IL-1β concentration than pregnant cows (Manjari et al., 2018). However, *in vitro* studies reveal that IL-1 modulates the production of luteotrophic PGE2 and luteolytic PGF2α locally in bovine CL as well as in endometrium (Nishimura et al., 2004; Tanikawa et al., 2005). IL-1α is believed to be more potent towards PGE2 production as compared to IL-1β (Tanikawa et al., 2008) and the luteotrophic action is modulated by IFNτ during early pregnancy which may support implantation and early embryonic development in bovines (Majewska et al., 2010). PGE2 not only sustains the progesterone production by its luteo-protective action but also down-regulates IL-2 expression in bovine PBL to maintain the pregnancy (Emond et al., 1998). IL-2 is a pro-inflammatory cytokine and is known to be a T cell growth and differentiation factor (Ross and Cantrell, 2018). How IL-2 affects T cell population during bovine pregnancy is largely unknown.

However, higher plasma IL-2 concentration was noticed in cows which exhibited early embryonic mortality and late embryonic mortality as compared to pregnant cows (Panda et al., 2020). IL-4 being an anti-inflammatory cytokine and a key regulator of innate as well as adaptive immune system causes differentiation of naive helper T cells (Th0 cells) to Th2 cells (Seder et al., 1992). In addition to this IL-4 increases its expression in a positive feedback manner and decreases the expression of IFNγ in a negative feedback loop. Higher expression of IL-4 during pregnancy is necessary for embryo implantation which is modulated mainly by IFNτ (Tuo et al., 1999) and progesterone (Maeda et al., 2013). IL-6 acts as both pro and anti-inflammatory cytokine. It is known to increase the inner cell mass of bovine embryo (Wooldridge and Ealy, 2019) and along with leukemia inhibitory factor; IL-6 induces the proliferation and attachment of porcine trophoblast cell during early pregnancy (Blitek et al., 2012). Contrary, around 18 days post AI, non-pregnant cows displayed higher plasma IL-6 level as compared to the pregnant cows (Mohammed et al., 2017). IL-8 is a pro-inflammatory cytokine and is known to be a potent chemoattractant for neutrophil towards the inflammatory site. Besides their pro-inflammatory activity, they also promote angiogenesis in the developing CL (Jiemtaweeboon et al., 2011). Higher plasma IL-8 levels have been shown to increase the immune response towards the implanting embryo thus resulting in implantation failure in bovines (Sheikh et al., 2019). Being an anti-inflammatory cytokine, IL-10 puts a break on the innate and adaptive immune system and limits tissue damage due to inflammation (Ouyang et al., 2011). Pregnant bovine endometrium demonstrates an increase in IL-10 expression which is necessary for the maintenance of the pregnancy (Oliveira et al. 2013). According to Shirasuna et al. (2012), increased IL-10 expression in PBMCs is enhanced mainly due to IFNτ stimulation. Whatsoever may be the mechanism behind the cytokines mediated maternal immune modulation, it is imperative that without an orchestrated balance between pro-inflammatory and anti-inflammatory cytokines, the success in pregnancy can never be achieved.

Th2 bias during early pregnancy establishment:

Wegmann and colleagues reported that there is biasness towards the Th2 cytokine pathway during pregnancy which promotes tolerance towards the half foreign fetus (figure-1). Moreover, Th1 cytokines are regarded as harmful for the tolerance of semi-allogeneic fetus which is similar to allografts in transplant recipients (Wegmann et al., 1993; Erdmann et al.,

2004). It has been well documented that during the induction of tolerance to the allograft tissue there is an increase in Th2 cytokines including IL-4 and IL-10 and a decrease in Th1 cytokines such as IL-2 and IFNγ. Conversely, the allograft gets rejected when there is a high level of IL-2 and IFNγ (Strom et al., 1996; Li et al., 1998). One of the interesting *in vitro* study conducted by Mao and co-workers (2010), revealed that when T-reg cells purified from pregnant women were cultured with paternal or unrelated PBMCs, T-reg cells caused the suppression of the inflammatory cytokine IFNγ which ultimately inhibited the inflammatory type 1 (cell-mediated) immune responses.

Many of the scientists believe that the Th2 bias in pregnancy is an oversimplified concept and there is a dynamic modulation of pro and anti-inflammatory cytokines that exist during various stages of pregnancy. In general, the pregnancy has been categorized into three important stages according to the predominant cytokines milieu in different stages of pregnancy. The first stage of pregnancy is the implantation of the blastocyst into the mother's uterus which is predominantly a pro-inflammatory phase. In this stage, the mother's immune system tries to accommodate the alien antigens. The second stage of pregnancy which is the phase of growth and development of the fetus is predominantly an anti-inflammatory phase. Th2 cytokine bias during this stage can be systemic or local at the feto-maternal interface. The last stage of pregnancy is parturition in which expulsion of the fetus occurs by contraction of the uterus and again the pro-inflammatory milieu is predominant at this stage. During all the stages of pregnancy, the process of inflammation is tightly regulated by the maternal immune system and failure in regulation during any stage will result in adverse pregnancy outcomes.

Microarray analysis performed by Walker and colleagues (2010), revealed 1,839 and 1,189 differentially expressed transcripts in the caruncular and intercaruncular endometrium respectively between the pregnant and cyclic Holstein-Friesian dairy cattle. In their study, they observed up-regulation of the chemokine receptor CXCR3 ligands (CXCL9, CXCL10 and CXCL11) and downregulation of the CXCR3 receptor in pregnant animals. The CXCR3 receptor is primarily expressed on Th1 cells (Patel et al., 2001) and its downregulation in pregnancy suggests that either Th1 cells were not increased in the uterus or the Th1 cells are not expressing CXCR3 receptors during the implantation window. It has been observed that the population of uterine NK (uNK) cells dramatically increases in maternal decidua during early pregnancy and continues to increase up to the end of the first trimester of pregnancy (Bulmer et al., 1991; Lee et

al., 2011). These uNK cells also express CXCR3 receptors on their cell surface (Sentman et al., 2004) and up-regulation of this receptor's ligand may have a role in the activation of uNK cells in the uterus during pregnancy and thus initiating an innate immune response at the feto-maternal interface so as to protect the mother from exogenous infections. Besides CXCs, there are several other chemokines such as CCL11, CCL2, CCL8, etc. which attract immune tolerance promoting immune cells like Th2 cells and NK cells during early pregnancy (Walker et al., 2010). Up-regulation of chemokine CCL11 attracts CCR3 (Receptor of CCL11) expressing Th2 cells (Dominguez et al., 2003) and CCL2 chemokine up-regulation attracts leucocytes which express its receptor i.e., CCR2 (Dominguez et al., 2003; Meter et al., 2005). Another chemokine CCL8 also known as monocyte chemo-attractant protein 2 (MCP2) is responsible for attracting monocytes, NK cells, lymphocytes, eosinophils and basophils through bindings of its receptor CCR1, CCR2, CCR3 and CCR5 during implantation (Hannan and Salamonsen, 2007). CCL8, CCL2 along with chemokine receptor CX3CR1 are actively involved in leukocyte recruitment and neovascularization during wound repair (Ishida et al., 2008; Balaji et al., 2015). In addition to chemokines, several interleukins such as IL-15, IL-7, and TGFβ also play a significant role in the establishment of pregnancy. IL-15 induces the proliferation of immune tolerance promoting T-reg cells in the uterus of the pregnant animals which shifts the inflammatory response towards the anti-inflammatory pathway (Guerin and Robertson, 2009). Likewise, the up-regulation of IL-7 in the pregnant endometrium enhances growth and survival-promoting factor for T-reg cells (Harnaha et al., 2006). Although, the role of different Th1 and Th2 cytokines in the context of bovine pregnancy needs to be more precisely investigated, but, these preliminary ideas points towards a Th2 bias during the establishment of bovine pregnancy.

Role of interferon-stimulated genes (ISGs) during pregnancy:

Another group of scientists (Bauersachs et al., 2006; Mitko et al., 2008; Mansouri-Attia et al., 2009) also reported an up-regulation of interferon-stimulated genes (ISGs) in pregnant animals. Among ISGs, the up-regulation of the OAS gene during early pregnancy is involved in the regulation of osteopontin (SPP1) production (Spencer et al., 1999; McAveney et al., 2000). SPP1 up-regulation in pregnant animals may have several crucial functions which include the promotion of trophoblast adhesion to the maternal endometrium, stimulation of morphological changes in the trophoblast and regulation of the immune response (Johnson et al., 2003). Various

immune cells like NK cells, macrophages, monocytes and T-lymphocytes express SPP1 which is believed to regulate the Th1/Th2 balance and apoptosis (Johnson et al., 2003). At this critical immunosuppressive stage of pregnancy, the mother also needs to protect her from pathogenic infections and this protection is facilitated by the up-regulation of some other ISGs like MX1 and MX2. It has been hypothesized that to encounter the potential viral pathogens during the time of local immune suppression mother's uterus express MX1 and MX2, suggesting that the innate immune system is active during early pregnancy (Hicks et al., 2003). Beside uterus, it has been reported that peripheral blood leucocytes also express MX2 during pregnancy (Gifford et al., 2007).

In addition to ISGs, there are several additional ISGs like IFITM1, Peptide Transporters (TAP-1 and TAP-2), MHC I A, and MHC I G which may have the function to provide localized immune system suppression that allows the embryo to survive within the uterus (Walker et al., 2010). IFITM1 acts as an immunomodulatory molecule and up-regulation of this gene is believed to be linked with immune-modulation of NK cells (Yang et al., 2005) thus create an immunosuppressive milieu during the implantation period. It has been observed that the local immune suppression is also associated with the up-regulation of TAP proteins, as the up-regulation of TAP-1 protein is involved in the transformation of natural killer cells to become non-cytotoxic (Kalkunte et al., 2009). According to Kalkunte et al. (2009), this transformation of NK cells is achieved through the expression of vascular endothelial growth factor-C (VEGF-C) which with the help of induction of TAP-1 protein enhances the resistance of trophoblast and endothelial cells to lysis. These findings demonstrate and highlight the necessity of maternal immune-modulation during early pregnancy and the fundamental requirement of a delicate balance between Th1/Th2 cytokines along with the pivotal importance of ISGs during early pregnancy establishment in bovines.

3. Role of indoleamine 2, 3-dioxygenase (IDO) in fetal immune-tolerance

Pregnancy exhibits a complex phenomenon in which a delicate balance between pro and anti-inflammatory cytokines is needed to maintain maternal immune system integrity while preventing rejection of the embryo. In this critical process, IDO plays an important role in shifting these cytokines according to the need of the maternal immune system. IDO is the first and rate-limiting enzyme of the tryptophan catabolism via the kynurenine pathway which is the major route of L-tryptophan catabolism and a mechanism for nicotinamide adenine dinucleotide

(NAD+) synthesis in mammalian tissues. IDO converts tryptophan into N-formyl-kynurenine which is then converted into several biologically active metabolites like 3-hydroxykynurenic acid, 3-hydroxyanthranilic acid and quinolinic acids (Stone and Darlington, 2002). IDO is an intracellular enzyme and to date, none of its secreted or extracellular forms has been identified. Evidence shows that IDO is expressed at the maternal-fetal interface, including trophoblast cells, decidual stroma cells, decidual immune cells (e.g., natural killer cells, T cells, and macrophages), and vascular endothelial cells of decidua and chorion (Kudo et al., 2004; Von Rango et al., 2007).

A novel IDO paralogue known as indoleamine 2,3-dioxygenase-2 (IDO2), was discovered independently by several groups (Ball et al., 2007, Metz et al., 2007) in 2007. It is not only present in mammals but also found in lower vertebrates. It is named based on its structural similarity and enzymatic activity to 'conventional' IDO (referred to as IDO1). The IDO1 and IDO2 enzymes share a similar range of substrates (Ball et al., 2007), while they differ in some biological functions, for instance, their selectivity for inhibitors. The selective inhibition of IDO2 is 1-methyl-D-tryptophan, while 1-methyl-L-tryptophan is a better inhibitor of IDO1 activity (Ball et al., 2009). As most of the studies in the literature have not specialized the role of IDO1 and IDO2 separately, the term "IDO" will refer to the collective functional IDO enzyme activity, unless otherwise specified. Apart from IDO, another tryptophan degrading enzyme is tryptophan 2,3-dioxygenase (TDO). TDO is widely distributed in both eukaryotes and bacteria whereas, IDO has only been found in mammals and yeast.

The regulatory mechanism of IDO expression has been studied thoroughly by different groups of scientists and substantial evidence suggests a complex counter-regulatory mechanism of IDO expression at the feto-maternal interface. Researchers have revealed that IDO expression is initially induced by certain pro-inflammatory molecules like IFNγ (most potent IDO stimulator) produced from the T-cell activation (Miwa et al., 2005). This finding is well correlated with the previous discussion in the review that the first phase of the pregnancy is a pro-inflammatory phase. However, once the expression of IDO becomes significantly high, it may counter-regulate the inflammatory molecules by suppressing the alloreactive T-cells and skewing their differentiation towards immunosuppressive T-regulatory cells (Mezrich et al., 2010). At this stage, the innate immunity of the mother takes over the charge and prevents the mother from pathogenic infection (Hicks et al., 2003) with simultaneous protection of the

allogeneic fetus. The detailed mechanism behind the IFNγ mediated IDO up-regulation remains unclear. However, it is reported that IFN-γ induces Janus-activated kinase (JAK)/STAT1 and protein kinase Cδ (PKCδ) signaling and blocking this pathway resulted in the suppression of IDO expression in cancer cells (Jeong et al., 2009; Cheng et al., 2010). Nevertheless, these findings provide us a clue about the possible mechanism behind IDO expression due to IFNγ production in early pregnancy (Boyt et al., 2020).

In 1998 immunostaining technique performed by Munn and co-workers revealed that there is a high level of IDO staining in the syncytiotrophoblasts of the placenta (Munn et al., 1998; Mellor and Munn, 2001). They hypothesized that increased IDO expression in the placenta plays a significant role in the prevention of the semi-allogeneic fetal rejection during early pregnancy. In support of their hypothesis, they used IDO inhibitor (1-methyl-tryptophan) at the pharmacological range and observed a rapid T-cell mediated rejection of allogeneic fetus (Munn et al., 1998). Since then, the mechanism behind the immunosuppressive action of IDO in successful pregnancy has been explored by several immunologists. The most accepted and widely used theory behind the immunosuppressive action of IDO is based on the tryptophan depletion theory (Mellor and Munn, 1999; Munn et al., 1999). According to this theory, overexpression of IDO in certain types of cells will consume the available tryptophan in the microenvironment; as a result, the neighboring maternal T-cell will starve of this essential amino acid. Subsequently, the deficiency of tryptophan blocks the progression of the cell cycle in activated T-cells which leads to T-cell arrest at the mid-G1 phase of the cell cycle and the cells undergo apoptosis (Lee et al., 2002). This process leads to immunosuppression due to the inhibition of locally activated T-cell proliferation. Schematic representation of IDO mediated maternal immunosuppression in bovines has been depicted in figure-2.

Tryptophan depletion theory has been supported by some experimental observations for instance Mellor et al, reported that up-regulation of IDO expression in dendritic cells restricted T-cell clonal expansion along with rapid death of activated T-cells (Mellor et al., 2004). However, when tryptophan was supplied in excess the T-cell responses were restored. This tryptophan starvation due to IDO expression also affects the neighboring cytotoxic T-cells and reduces its cytotoxicity via downregulating the T-cell receptor (TCR) zeta-chain (Fallarino et al., 2006). It has been studied that depletion of tryptophan activates certain kinases like general control non-repressed 2 (GCN2) kinase which suppresses glycometabolism and proliferation of

alloreactive T-cells, thereby causing immunosuppression at the feto-maternal interface (Eleftheriadis et al., 2013; Eleftheriadis et al., 2014).

With the increasing knowledge and research related to the IDO mechanism, the immunologists explored yet another mechanism of IDO immune-tolerance which is mediated by the biologically active metabolites of kynurenine produced during the process of tryptophan catabolism (Terness et al., 2007; Badawy et al., 2016). Kynurenine is a tryptophan metabolite that behaves like an endogenous ligand for the activation of aryl hydrocarbon receptor (AhR) (Opitz et al., 2011; Liu et al., 2017). Upon activation of this receptor along with TGFβ exposure a cascade of signaling pathway is generated which skews the differentiation of alloreactive T-cells to immunosuppressive Foxp3+ T regulatory cells (Nguyen et al., 2010; Mezrich et al., 2010). Interestingly, this AhR signaling has also been shown to induce IDO expression and activates 2 metabolites of kynurenine (kynurenic acid and xanthurenic acid) which ultimately participate in the process of immune-suppression during early pregnancy (Jaronen and Quintana, 2014; Fazio et al., 2017; Nguyen et al., 2014). Other metabolites like 3-hydroxyanthranilic acid (3-HAA) and quinolinic acids also affect the T-cell population. It has been reported that these metabolites activate caspase 8 and releases cytochrome-c from the mitochondrial matrix which can induce the selective apoptosis of Th1 cells rather than Th2 cells (Fallarino et al., 2002). 3-HAA can also cause immunosuppression directly by inhibiting the activation of dendritic cells and phosphoinositide-dependent kinase-1 (PDK1) along with depletion of intracellular glutathione levels, ultimately leading to T-cell apoptosis (Hayashi et al., 2007; Lee et al., 2010). Other tryptophan metabolites like 3-hydroxykynurenine (3-HK) and picolinic acid have also been observed to cause immunosuppression during pregnancy; however, their mechanism of action remains unclear (Zaher et al., 2011; Prodinger et al., 2016).

Beside IDO expressing immune cells, there are some non-immune cells like fetal trophoblast cells, maternal endometrial/decidual stromal cells which also express IDO during pregnancy and play a pivotal role in maternal-fetal tolerance. IDO expressing fetal trophoblast cells remain in close proximity to the maternal immune system and suppresses the proliferation of alloreactive T-cells (Dong et al., 2008). It also reduces the Th1/Th2 cytokine ratio at the feto-maternal interface during pregnancy, thereby switching the cytokine profile towards the Th2 pathway (Li et al., 2007). Apart from immunological modulation by IDO expression in trophoblast, IDO can directly influence fetal trophoblast in terms of its proliferation and

migration which has been observed to be mediated via the STAT3 signaling pathway (Zong et al., 2016). Meanwhile, the maternal decidual stromal cells also express IDO which induces macrophage tolerance via IL-33, thereby reducing the phagocytic ability of the macrophages (Mei et al., 2014). These IDO expressing stromal cells also affect the proliferation, cytotoxicity and cytokine production of NK cells and prepare the endometrium to become receptive for the implantation of the semi-allogeneic fetus (Croxatto et al., 2014).

Numerous studies have also been conducted in relation to pathological pregnancy in which the role of IDO has been implicated. In the case of recurrent spontaneous abortion (RSA), it has been documented that the level of IDO expression at the maternal-fetal interface is profoundly low as compared to normal pregnancy (Ban et al., 2013). Along with low IDO expression, there is also a reduction in STAT3 phosphorylation and MMP9 expression observed in RSA patients which indicates an imbalance in the IDO-STAT3 pathway (Zong et al., 2016). As mentioned earlier that the most potent stimulator of IDO expression is IFNγ, the production of this cytokine by decidual and peripheral blood mononuclear cells were surprisingly found to be low in RSA patients resulting in a low level of IDO expression and activity (Miwa et al., 2005) thereby leading to failure of pregnancy. A similar trend has been observed in the case of preeclampsia in which there is a reduction in IDO expression and activity leading to diminished numbers of Foxp3+ T-reg cells (Liu et al., 2011) and thereby leading to pregnancy failure. These findings highlight the essential role of IDO expression at the feto-maternal interface to achieve fetal immune tolerance during a successful pregnancy. However, there is still insufficiency of the detailed mechanism behind IDO immunosuppression that exists in normal pregnancy and extensive future study is needed to explore the immune-regulatory action of IDO at the maternal-fetal interface.

Conclusion:

To meet the increasing demand of the growing population in terms of milk and beef requirements, the production potential of cattle has to be improved. As production is directly related to the reproduction, therefore improving reproductive efficiency of cattle is the need of the hour. However, embryonic mortality, failure of successful implantation, fetal rejection due to undue maternal immune system activation etc., are some of the major elements to derail its success by production, reproduction and economic mean. Nutritional, genetical, climatic,

endocrine, inappropriate uterine environment, pathological agents are the major issues known to be the predisposing factors for low reproductive efficiency in bovines. Moreover, improper maternal immune activation might be another area which needs to be explored comprehensively in bovines. Understanding the embryo-maternal bidirectional communication thorough different approaches/ techniques might help us to decode it and some strategic measures like use of immune-modulators, identification and selection of immune-competent breed, development of some mathematical models to diagnose poor reproductive efficiency might be useful for formulating as well as adopting different cattle breeding and management policy. Understanding the different mechanisms behind bovine pregnancy establishment will not only help to prevent the embryonic mortality but also will reduce the non-pregnancy period in the cattle. Although the basic research on bovine reproductive immunology is expanding, the extent and intensity of maternal immune modulation by different cellular and humoral factors during bovine pregnancy remains elusive. Thus, further research is needed to ensure better immune management practices during transition and post partum stages of bovine so as to improve reproductive efficiency and thereby to achieve optimal production potential in bovines.

Conflict of interest:

None declare

Acknowledgement:

None declare

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Captions:

Figure-1: Schematic representation of Th1-Th2 cytokine balance during pregnancy.

Figure-2: Schematic representation of indoleamine 2,3 dioxygenase (IDO) mediated maternal immunosuppression in bovines.

Table-1: Gestation length, placentation days, agents of MRP and day of production of MRP agents in different species