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Review article

Immune status during postpartum, peri-implantation and early pregnancy in cattle: An updated view

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ABSTRACT

Throughout the estrous cycle the mammalian endometrium undergoes morphological and functional changes that are essential for the establishment of pregnancy and proper ovarian and uterine functions. Among these changes, the most important are alterations in both inter- and intracellular signalling molecules, many of which modulate immune processes. In the endometrial tissue there are local innate (nonspecific) and adaptive (specific/acquired) response mechanisms which vary because of the endocrine status during the estrous cycle, pregnancy and postpartum period. Endometrial cells have responses that support the immune system by producing pro-inflammatory factors such as cytokines, sensors, effector molecules and chemokines. This response is important during gestation, pregnancy, and fetal growth, as well as in preventing infection, and immuno-rejection of the semi-allogeneic embryo. In dairy cows, both before and immediately after calving, there are marked changes in the values for hormonal and metabolic variables and the immune status is impaired. Thus, in several studies there has been assessment of the physiological and/or abnormal maternal immune changes and possible effects on dairy cow reproductive performance. The objective with this review is to summarize the novel information about the immune mechanisms involved during the postpartum period, subsequent peri-implantation period and pregnancy in dairy cows, and the possible effects on reproductive performance. This information provides for an enhanced understanding of the local and systemic immune responses associated with the metabolic and hormonal status of dairy cows, and alterations in the immune system of high producing cows and the possible effects on subsequent fertility.

1. Introduction

Throughout the estrous cycle, the endometrium of mammals undergoes morphological and functional changes that are important for the establishment of pregnancy. Uterine functions such as implantation and placental growth are complex processes tightly regulated by the interaction between the endocrine and immune systems. There is increasing evidence that this interaction is essential

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for effective ovarian and uterine functions (Henderson et al., 2003; Tekin and Hansen, 2004; Padua et al., 2005; McDonald et al., 2006).

In reproductive tissues, steroids (such as progesterone and estradiol) and local cell signaling molecules (such as cytokines) have immune functions. In several studies there have been reports that estradiol-17β and progesterone have pro- and anti-inflammatory functions in several organs, respectively (Hunt et al., 1997; Tibbetts et al., 1999; Maeda et al., 2013). In addition, in cows and rats with abnormal ovarian function such as cystic ovarian disease there is an altered expression of estrogen receptor genes (Salvetti et al., 2007, 2009). With regard to signalling molecules, ovarian follicles at different developmental stages in estrous-synchronized healthy cows had an immuno-induced expression of several cytokine genes both in granulosa and theca cells (Baravalle et al., 2015; Stassi et al., 2017). Cytokines function in the intra-ovarian cell communication and possible endocrine regulation of ovarian functions.

The differential functions of the endocrine and immune systems in reproductive biology and the effects on fertility are still unclear (Lewis, 2004; Walsh et al., 2011). Results from earlier studies indicate that treatment of ovariectomized cows with estradiol-17β or progesterone had no significant effect on alterations in uterine polymorphonuclear leukocyte functions, whereas treatment with estradiol-17β of cows at estrus leads to greater polymorphonuclear leukocyte functions (Lander Chacin et al., 1990; Lewis, 2004; Sheldon et al., 2010). Similarly, progesterone has an important function on fertility, especially in the establishment and maintenance of pregnancy. In several studies (McNeill et al., 2006; Diskin and Morris, 2008; Forde et al., 2009), with both beef heifers and dairy cows, there were positive correlations between the relatively greater concentrations of P4 and immune functions in the immediate post-conception period. All of these findings indicate the endometrium of cattle is remodeled throughout the estrous cycle and the most important changes are alterations in both inter- and intracellular signalling molecules, many of which effect immune processes and regulate the immune response. Endometrial luminal epithelial cells respond to and support the immune response by producing pro-inflammatory factors such as cytokines and chemokines (LeBlanc et al., 2011; Peter et al., 2015). The endometrial tissues have local innate (nonspecific) and adaptive (specific/acquired) response mechanisms, which change with the endocrine status during the estrous cycle, pregnancy and postpartum period. The uterine immune system of cows has important functions during gestation in maintaining pregnancy and for fetal growth and infection prevention (Ishikawa et al., 2004; Singh et al., 2008). Both before and immediately after calving, when there are marked changes in values for hormonal and metabolic variables, the immune status is seriously impaired. For example, there is a marked increase in cortisol concentrations that leads to leukocytosis during calving and infectious diseases are more prevalent around the time of parturition (Preisler et al., 2000).

The objective of this review is to summarize the novel information about the immune mechanisms during the postpartum period, peri-implantation period, and pregnancy in dairy cows, and possible effects on reproductive performance. This information will allow for a greater understanding of the local and systemic immune responses that are related to the metabolic and hormonal status of dairy cows, during physiological conditions such as resumption of ovarian functions, fetal implantation or lactation and the possible effects on subsequent fertility.

2. Immune status during the postpartum and puerperium periods and associations with the endometrial environment

In the reproductive tract of cows, there are multiple defense mechanisms against microorganisms. These mechanisms facilitate the return of physiologic functions of animals after there has been a disruption in typical physiologic processes to a homeostasic state (Medzhitov, 2008). In several studies, there has been examination of the expression of genes in samples collected either by endometrial biopsies or with use of the cytobrush, of the endometrial surface when there is a hormonal stimulus or/and comparison of gene expression between animals with a uterine disease or inflammation and healthy animals during the early postpartum period (Chapwanya et al., 2012; LeBlanc, 2012; Sheldon et al., 2014; Peter et al., 2015). The regulated mechanisms of tissue repair and recovery of activity and reproductive function of the endometrium include both local and systemic immune defenses (Fig. 1).

2.1. Non-specific defenses: anatomical barrier and involvement of cytokines in uterine involution

Epithelial cells throughout the female reproductive tract constitute the first anatomical and physiological barrier to infectious agents. If infectious agents breach this barrier, therefore, specialized immune cells and endometrial cells rapidly respond as a result of activation of different mechanisms (Wagner and Hansel, 1969; Dadarwal et al., 2017). Endometrial cells have toll-like receptors (TLR) for detection of bacterial ligands, such as peptidoglycans and lipopolysaccharides (Sheldon et al., 2014; Turner et al., 2014; Dadarwal et al., 2017; Sheldon et al., 2018). The activation of TLR initiates signalling cascades, followed by the synthesis and production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα). Subsequently, TNFα functions to promote the migration of specialized immune cells from the blood to the uterine tissues (Sheldon and Dobson, 2004; Kim et al., 2005). There is also a rapid and robust innate immune response including the secretion of cytokines from the endometrium, such as interleukins (IL) 1β and IL6, and chemokines, such as IL8 (Hammon et al., 2006; Singh et al., 2008; Cronin et al., 2012; Peter et al., 2015).

There is function of TNFα as a potent stimulator of prostaglandin F2α ($PGF_{2\alpha}$) secretion in the cattle endometrium cultured *in vitro* which may lead to alteration in fertility by interfering with the production or action of hormones in the endometrium and ovarian follicular cells of cattle (Spicer, 1998; Skarzynski et al., 2000; Herath et al., 2009). Furthermore, the activation of $PGF_{2\alpha}$ receptor may induce endometrial repair by upregulating prostaglandin synthase (PTGS) 2 gene expression and stimulating TGFβ1 and IL8 gene expression (Gao et al., 2018; Zhang et al., 2018). There is also IL1α modulation of endometrial $PGF_{2\alpha}$ secretion during the period when these changes in gene expression are occurring that results in and increase lymphocyte responses and stimulation of the production of acute-phase proteins (APPs) from epithelial cells (Leung et al., 2001; Tanikawa et al., 2005; Herath et al., 2009). These processes could contribute to regulating the inflammation and induction of anti-inflammatory responses (Fig. 1).

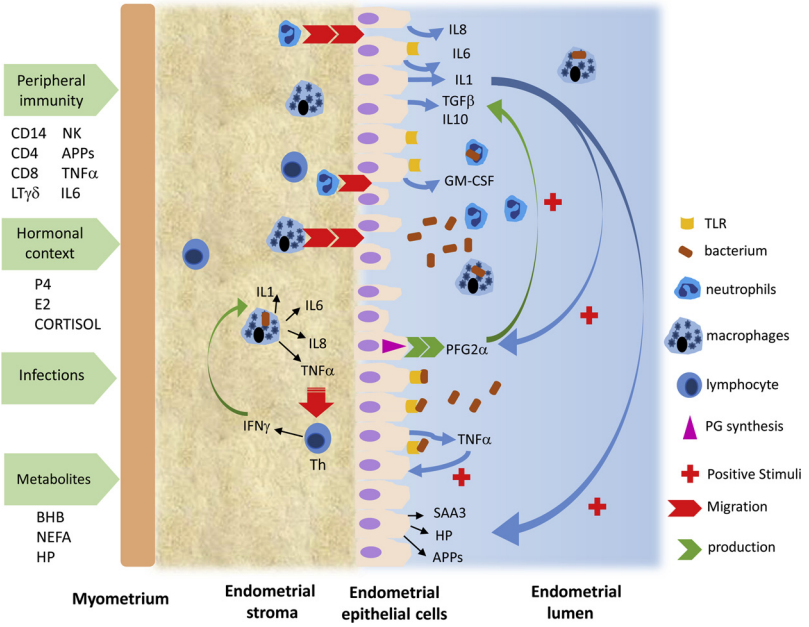

Fig. 1. Early postpartum uterine environment. During the early postpartum period there are regulated mechanisms underlying tissue repair and recovery of reproductive function of the endometrium including non-specific pro-inflammatory cytokine IL1, IL6, TNFα, and systemic actions on macrophages, LT, LB and NK cells. Endometrial cell response to bacterial infection occurs as a result of TLR activation and signalling cascades to the synthesis and production of pro-inflammatory cytokines, such as TNFα. TNFα that promotes the migration of specialized immune cells from the blood to the uterine tissue (macrophage, neutrophils, lymphocyte), and induces a rapid and robust innate immune response of the endometrium in production of interleukins (IL)1β and IL6, and chemokines, such as IL8, and APPs. Regulation of this rapid response could occur as a result of PG synthesis and TGFβ production by endometrial epithelial cells.

2.2. Cytokines and acute phase proteins: involvement in postpartum inflammation and endometritis

The APPs, likely stimulated by IL1, may provide further *in situ* protection against infections especially during the peripartum period (Sheldon et al., 2001; Chapwanya et al., 2009, 2012). Although it is likely that hepatic production of APPs may be more relevant *in vivo*, Chapwanya et al. reported there were changes in haptoglobin (HP) and serum amyloid A3 (SAA3) gene expression at 15 days postpartum (DPP) in endometrial tissues, relative to that observed at 60 DPP (Chapwanya et al., 2012). It was also observed that, at 30 DPP, there was a significant reduction in the expression of all the innate immune genes that were analyzed (markers, sensors, mediators, effector molecules), which is consistent with findings related to inflammation that were detected histologically. Because the pro-inflammatory cytokines, IL1β and IL6, regulate inflammatory responses and the production of APPs (Andus et al., 1988), Chapwanya et al. found that the expression of these genes is increased at 15 and 30 relative to 60 DPP (Chapwanya et al., 2012). Likewise, there was an increase in the abundance of mRNA for the mediators, TNFα and IFNγ, and the chemokine IL8 in all the animals at 15 and 30 relative to 60 DPP. These findings indicate, both with assessments of histology samples and gene expression, that the inflammatory endometrial response after calving is reduced, and that the process is tightly regulated (Pioli et al., 2004; Schaefer et al., 2004; Chapwanya et al., 2009). Hence, the increased TNFα, IL1β and IL6 gene expression, which regulate SAA3 and HP production is altered for restoration of uterine homeostasis and optimal uterine conditions for pregnancy to occur (Hiss et al., 2004), which probably implies the induction of an anti-inflammatory response in the endometrium that is regulated by IL10 and TGFβ actions.

For the endometrium, there have been some studies evaluating the puerperal effects on the health status of the uterus of cattle that focused on the changes in abundance of mRNA for pro-inflammatory factors with the results indicating clinical and subclinical endometritis at 45 to 51 DPP result in a greater inflammation than at earlier stages in the postpartum period (Peter et al., 2015). These findings are consistent with the results of Galvão et al. where there was an increase in abundance of IL1β, IL6 and IL8 mRNA in uterine biopsies from cows with endometritis on week 7 after calving (Galvão et al., 2011). The expression of genes for important enzymes involved in the synthesis of prostaglandin (PG), such as PTGS1, PTGS2 and PTGDS, was affected, however, by the uterine health condition at 45 to 51 DPP. The PG production, therefore, appears to delay the inflammatory response (Peter et al., 2015) or to regulate the pro-inflammatory environment by means of the activation or synthesis of anti-inflammatory cytokines such as IL10 or TGFβ. In addition, Herath et al. reported that when there was comparison of the rates of transcription of genes involved in the innate immune response, particularly cytokines, there were infertile animals with persistent endometritis that had greater ratios for the abundance of mRNA for pro-inflammatory cytokines such as IL1α or IL1β and the abundance of mRNA for the anti-inflammatory cytokine, IL10, than animals with no clinically detectable disease (Herath et al., 2009).

2.3. Involvement of the metabolic status in the endometrial inflammatory response

Some uterine diseases are associated with changes in the metabolism after calving because dairy cows do not consume enough nutrients to meet the substantial demand required for lactation resulting in a negative energy balance (NEB). Consequently, as tissues are catabolized to provide the dietary energy and protein nutrients, cows lose body weight (Chagas et al., 2007; Sheldon, 2015). The cows with NEB that develop ketosis have lesser blood concentrations of glucose and relatively greater non-esterified fatty acid (NEFA) and β-hydroxybutyrate (BHB) concentrations. Studies are now being focused on the study mechanisms through which a different extent of NEB leads to suppressed immune responsiveness or excessive inflammation (Ingvartsen and Moyes, 2013). When there is relatively greater concentrations of NEFA, there is impairment of endometrial function as a result of decreasing cell viability and proliferation and increasing apoptosis (Chankeaw et al., 2018). When there are relatively greater concentrations of the NEFA, there is greater IL8 production from the endometrial epithelial cells of cattle *in vitro*. Interestingly, Zhang et al. (2018) reported that relatively greater concentrations of NEFA were positively correlated with pro-inflammatory cytokines because of the greater activation of TLR2 and TLR4 gene expression induced by the NF-κB inflammatory pathway in neutrophils of ketotic cows (Zhang et al., 2018). These findings indicate there may be a signaling mechanism through which NEFA induce the production of inflammatory cytokines from endometrial cells because of expression of genes for TLR. Regarding other metabolites, Turner et al. reported that there was a depletion of glucose in the presence of glutamine with the outcome being a decrease in the secretion of IL1β, IL6, and IL8 from cultured endometrial cells of cattle (Turner et al., 2016). These findings indicate that the decrease in endometrial glycolysis and consequently the intracellular energy source could lead to alteration in the inflammatory response to pathogens and increase the risk of uterine disease by impairing endometrial defenses (Sheldon et al., 2018).

In summary, the upregulation of the local immune response to control the bacterial infection, lochia production and uterine epithelium recovery has been considered a physiological process in the involution of the uterus during the postpartum period of cows. The length and severity of the immune response during the latter puerperium period may be a determining factor as to whether this process occurs as a transition from a physiological to a pathological status and/or if the subsequent fertility of the animals will be affected (Wathes et al., 2009; LeBlanc, 2012; Peter et al., 2015).

3. Systemic status of immunity during the peripartum period: an overview of the inflammatory context

3.1. Leukocytes, APPs and cytokines around calving

Total and peripheral blood leukocyte counts have been reported to increase during calving (Kim et al., 2005). At 1 week postpartum, total leukocyte counts decrease, and there is a return to greater numbers during the 3 weeks after parturition (Hussain and Daniel, 1992; Cai et al., 1994; Mateus et al., 2002; Kim et al., 2005). The increase in total leukocyte counts during calving could be due to an increase in cortisol concentrations (Preisler et al., 2000), while the decrease in total leukocyte counts postpartum has been related to the migration of leukocytes towards the mammary glands and uterine lumen (Guidry et al., 1976). There has been speculation that during the transition period (3 weeks prepartum until 3 weeks postpartum), dairy cows have a form of reduced immuno-competence. Heiser et al., however, have studied the cellular composition of blood from cows in the peripartum period and reported that the number of monocytes (CD14 +), T helper (CD4 +), cytotoxic T (CD8 +) and γδ T (WC1 +) cells do not change from pre- to post-calving sampling periods (Heiser et al., 2015). In addition, the number of NK cells (CD335 +) increases and the number of B cells (CD21 +) varies greatly between individual animals. Likewise, there are other reports where monocytes were more responsive to inflammatory conditions during the peripartum period than during other physiological states with there being increased cytokine concentrations during this period (Sordillo et al., 1995; McCarthy et al., 2016). Cytokines released by immune cells during inflammatory processes, such as TNFα and IL6, promote the production of APPs such as HP from the liver, as previously described (Hiss et al., 2004). Increased concentrations of HP during the early postpartum period have been related to reductions in reproductive functions (Huzzey et al., 2015). Systemic inflammation during the early postpartum period is characterized by increased concentrations of APPs in plasma (Bionaz et al., 2007; LeBlanc, 2012; McCarthy et al., 2016). This inflammation can be induced by pathogen recognition as well as by stress conditions such as calving or NEB during the early postpartum period. At the same time, increased plasma HP concentrations are associated with an increased innate leukocyte response (Nightingale et al., 2015). Both, the production of TNFα and the surface expression of L-selectin in neutrophils are greater in cows with greater HP concentrations. Furthermore, the increased incidence of animals with lesser reproductive performance during the subsequent lactation suggests the possible effects of inflammatory mechanisms in the homeorhetic adaptation to lactation, which could lead to impaired fertility (Farney et al., 2013; Nightingale et al., 2015).

3.2. Effects of metabolic changes on circulating immune cells and inflammatory response

Metabolic changes *in vivo* could affect the gene expression patterns of neutrophils during the peripartum period. Also, the overexpression of the IL1β gene around the time of calving appears to correlate with the marked metabolic alterations occurring during the transition period (Zhou et al., 2015). Because the innate immune response requires a large amount of energy for activation of immune cells and alterations in function of the endometrial tissue, there is a relatively lesser availability of glucose and as a result an associated perturbation of the immune response (Hammon et al., 2006; Wathes et al., 2009). Postpartum dairy cows undergoing metabolic stress also develop insulin resistance, have reduced concentrations of insulin-like growth factor 1 and glucose in blood, and have increased concentrations of ketones, such as acetoacetate and BHB, due to mobilization of fat reserves, which characterize the

metabolic profile of ketotic cows (Chagas et al., 2007; Wathes et al., 2011; Angeli et al., 2019). Zhang et al. (2018) studied the over-activation of the TLR2/4- NF-κB signaling pathway as a result of NEFA actions and it was reported that IL6, IL1β and TNFα were increased in neutrophils from ketotic cows (Zhang et al., 2018). Conversely, the inhibition of NF-κB action suppressed the NEFA-induced synthesis of pro-inflammatory cytokines. Taken together, these findings confirm that the ketotic metabolic milieu has a positive effect on the synthesis of pro-inflammatory cytokines in neutrophils of cows.

In addition, Kovacevic et al. (2018) reported that there is an association of metabolic and inflammatory markers with milk yield in postpartum dairy cows treated with ketoprofen, an anti-inflammatory drug (Kovacevic et al., 2018). In this previous study, keto-profen-treated cows had greater milk production and a lesser concentration of NEFA, BHB, TNFα and HP during the first and second week of the postpartum period (Kovacevic et al., 2018). Although it is known that metabolic stress compromises the peripheral blood immune cell functions of dairy cows during the postpartum period, the underlying biochemical and molecular mechanisms are somewhat obscure (Hammon et al., 2006; Mendonça et al., 2013; Sheldon, 2015).

4. Immune status during peri-implantation and pregnancy

As previously described in this manuscript, the persistence of bacterial infections in the endometrium and acute systemic inflammation during the early postpartum period induces perturbation of immune functions in cattle. Also, metabolic alterations during the peripartum period could prolong the time required for uterine recovery and compromise subsequent fertility (Wathes et al., 2009; Giuliodori et al., 2013; Ingvartsen and Moyes, 2013; Esposito et al., 2014). In this regard, several studies have been conducted to understand the mechanisms involved during the peri-implantation period and in the feto-maternal interface “crosstalk” in terms of immunity. The results of these studies are subsequently summarized and discussed.

4.1. Local immune response: signals from the conceptus

The main functions in pregnancy establishment and fetoplacental development are those related to uterine receptivity to the embryo, embryo implantation, and tolerance and viability of the conceptus inside the uterus. These uterine factors depend on paracrine and endocrine signals such as steroid hormones, interferon tau (IFNT) from the conceptus in ruminants, and the mediation of a network of cytokines from endometrial tissues and immune cells (Fig. 2) (Roberts et al., 1992; Rice and Chard, 1998; Mansouri-Attia et al., 2012). Alterations in these regulated mechanisms lead to embryonic loss during the first 4 weeks of gestation and, accordingly, are the main cause of pregnancy failure in dairy cattle (Inskeep and Dailey, 2005; Diskin and Morris, 2008).

The period during which conceptus signalling has to occur to maintain pregnancy is between days 15 and 18 of pregnancy, when IFNT is secreted by the conceptus to prevent the regression of the corpus luteum and to ensure a continuation of progesterone production beyond the typical functional period of the corpus luteum if pregnancy has not occurred (Bazer et al., 2008). Furthermore, IFNT, which is a type I interferon, is thought to be responsible for modifying uterine immune cell function to result in an optimal environment for embryo growth and development of a functional placenta (Ott and Gifford, 2010). Both uterine immune (Leung et al., 2000; Nagaoka et al., 2003; Forde and Lonergan, 2012; Oliveira et al., 2013) and circulating immune (Stevenson et al., 2007; Oliveira et al., 2008; Kamat et al., 2016) cells are responsive to IFNT. In this regard, the conceptus and other endocrine mediators, such as progesterone, function to regulate the maternal immune response during early pregnancy and relatively little is known about

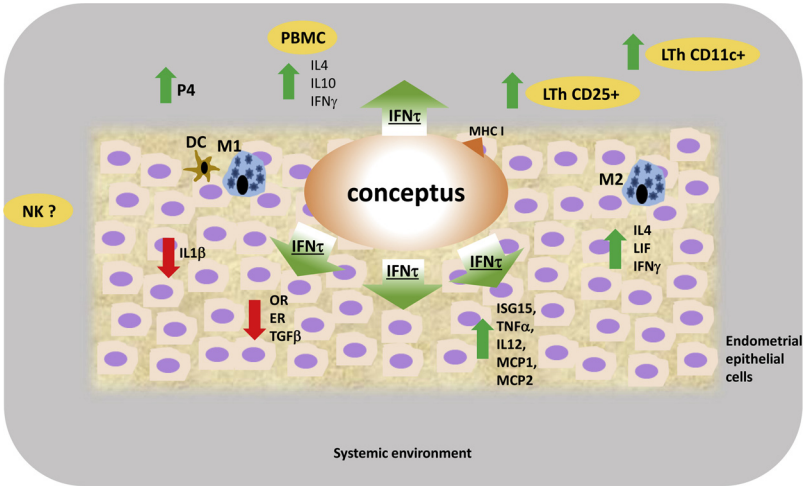

Fig. 2. Immune signals during the peri-implantation period and pregnancy in cows. The viability of the conceptus inside the uterus depends on paracrine and endocrine signals such as steroid hormones, IFNT from the conceptus and the mediation of a network of cytokines from endometrial tissues and immune cells. The positive effect of IFNT are depicted with green arrow and negative regulation with the red arrow. IFNT from the conceptus exerts actions in other tissues as well as at the uterus to modulate the systemic environment so as to enhance the probability of pregnancy occurring. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

this relationship. In different reports, it has been mentioned that the number of estrogen and oxytocin receptors is downregulated in luminal epithelial cells in response to IFNT, which eventually results in lesser concentrations of $PGF_{2\alpha}$ secretion. This series of reactions ensures that there is production of progesterone by the corpus luteum and adequate progesterone priming by the uterus for pregnancy establishment and support (Forde et al., 2011; Fair, 2015). These findings indicate there are paracrine and endocrine actions of IFNT during pregnancy recognition and establishment in ruminants (Hansen et al., 2017).

4.2. Maternal tolerance to pregnancy: endometrial signals

In addition to its anti-luteolytic function, IFNT apparently functions at the endometrium to enhance the expression of genes that regulate uterine receptivity and embryo development. The expression of IFN-stimulated genes (ISG), such as TNFα, ISG15, IL12B, PTX3, monocyte chemoattractant protein 1 (MCP1), and MCP2 has been found to be up-regulated in the endometrial tissue of cattle (Mansouri-Attia et al., 2012). Also, the proteins MCP1 and 2 are potent chemotactic factors for monocytes, and the maternal immune response during embryo elongation in cattle is characterized by the expansion of monocytes and dendritic cells (DCs) in the endometrial stroma as early as day 13 of pregnancy (Mansouri-Attia et al., 2012). Likewise, increased endometrial expression of the PTX3 gene may reflect recruitment and/or activation of monocytes/DCs that results in enhanced PTX3 gene expression. Because it has been previously reported that a PTX3 deficiency could compromise implantation in mice (Tranguch et al., 2007), these findings suggest a potential role for PTX3 during early pregnancy (Mansouri-Attia et al., 2012). In addition, the paternal antigen of the conceptus and major histocompatibility complex-I transcripts found in early-stage cattle embryos (Doyle et al., 2009) are responsible for the potential antigenicity and the probable cause of the early response of endometrial phagocytic cells and dendritic cells. The maternal response during pregnancy, however, can be regulated by the action of at least a subpopulation M2 of activated macrophages, which decrease the activation of anti-conceptus immune responses (Oliveira et al., 2010) and through several cytokines, including IFNγ, IL4, and Leukemia inhibitory factor (LIF) (O'Gorman et al., 2010; Al Naib et al., 2011). Additionally, LIF and IL10 regulate M1 macrophage activation (Conti et al., 1990; Svensson et al., 2011; Fair, 2015). Regarding implantation, Mansouri-Attia et al. (2012) reported that TGFβ2 endometrial gene expression is downregulated during this period in both cattle and sheep, which suggests that TGFβ2 is involved in trophoblast invasion during the implantation phase. During placentation, TGFβ2 gene expression, however, is increased (Fair, 2015; Mansouri-Attia et al., 2012), a change that may result in the recruitment of monocytes and the regulation of the inflammatory status (Wahl et al., 1987). Thus, TGFβ2 may be involved as a growth factor in proliferation during placentation, promotion of caruncular growth, and development of epithelial cells for placentome formation in cattle (Wahl et al., 1987; Graham and Lala, 1991; Fair, 2015).

Another factor involved in the feto-maternal "crosstalk" is TNFα (Guzeloglu-Kayisli et al., 2009; Haider and Knöfler, 2009; Correia-álvarez et al., 2015a). In numerous reports, there has been a description of the involvement of the TNF system during implantation (Roby et al., 1995; Groebner et al., 2010; Payan-Carreira et al., 2011). A study conducted by Muñoz et al. about the proteome of the early embryo-maternal communication in the uterus of cattle indicated that the 78-kDa isoform of TNF, which is upregulated in the endometrium, is downregulated in the uterine fluid when embryos are present (Muñoz et al., 2012). Because the addition of exogenous TNF inhibits early embryo development *in vitro* in cattle (Jackson et al., 2012), the removal of TNF from the uterine fluid observed *in vivo* as an endometrial response could be the mechanism to prevent harmful effects in the embryo (Correia-álvarez et al., 2015a). Muñoz et al. also reported that there was a decreased IL1β concentration in the uterine fluid of cattle during early pregnancy, which could potentially induce a downregulation of NF-κB gene expression and a suppression of the maternal innate immune response (Muñoz et al., 2012). The results indicate IL1β through the feto-maternal "crosstalk" mechanisms effect the IL1 system and the capacity for pregnancy to occur in cattle (Correia-álvarez et al., 2015b).

In summary, the maternal response is not immunosuppressed and conceptus is not immunologically inert because of the fetal expression of histocompatibility antigens (Davies et al., 2006; Ott et al., 2014). Although during pregnancy there is suppression of some immune functions in the uterus by inducing expression of molecules such as uterine serpin, which has suppressive effects (Hansen, 2007), there is little evidence that pregnancy leads to immunosuppression (Oliveira et al., 2012; Ott et al., 2014). Clearly, when pregnancy occurs there is a different stimulation of the immune system, which, unlike host-pathogen interactions, involves immune changes related to both the activation and suppression of immune functions.

4.3. Peripheral immune response during the peri-implantation period and pregnancy

In ruminants, immune modulation occurs, not only in the uterus, but also in the peripheral immune system during the peri-implantation period and pregnancy (Ott and Gifford, 2010; Kamat et al., 2016). The functions of T cells in implantation and the establishment of immune tolerance have been reported in experimental and human model animals (Sharma, 2014; Lash et al., 2016). Nevertheless, relatively little is known about NK cells and macrophages in ruminants, especially during early pregnancy. The changes in the abundance of myeloid lineage cells during pregnancy in dairy cattle have been studied after day 30 of pregnancy and the observations have been focused mainly on mid- to late-gestation (Oliveira and Hansen, 2008; Oliveira et al., 2010). The results of these studies indicate that the proportion of CD4+ cells that are positive for CD25 are increased during pregnancy and is associated with the subsequent changes in the number of peripheral leukocytes that occurs between days 33 and 34 of pregnancy in cows (Oliveira and Hansen, 2008). In addition, Kamat et al. (2016) have reported that the presence of a conceptus results in an increase in the number of myeloid lineage cells in peripheral circulation of dairy heifers around the time of maternal recognition of pregnancy (Kamat et al., 2016). The authors postulated that the greater proportion of CD14+CD11c+ cells in the peripheral blood are monocytes that will migrate to the endometrium and differentiate into dendritic cells. Furthermore, the increase in chemotactic

protein gene expression observed in the endometrium during early pregnancy could result in an attraction of these cells and induction of migration of monocytes into the uterus (Walker et al., 2010; Mansouri-Attia et al., 2012), and be a factor in preparation of the uterine milieu for pregnancy (Kamat et al., 2016).

Recently, Hansen et al. reviewed the systemic action and effects of IFNT on peripheral blood mononuclear cells (PBMC) in ruminants and observed that the IFNT from the conceptus functions in other tissues in addition to the uterus (Hansen et al., 2017). There have been reports as a result of several studies of an increase in ISG gene expression in PBMC, liver, corpus luteum and maternal tissues (Oliveira et al., 2008; Ribeiro et al., 2014; Meyerholz et al., 2016; Sinedino et al., 2017). In this regard, ISG gene expression is upregulated during early pregnancy in the PBMC of sheep (Yankey et al., 2001) and cattle (Han et al., 2006; Gifford et al., 2007). Furthermore, results of a recent study focused on differential expression of IFNγ, IL4 and IL10 genes in the PBMC during early pregnancy of cows indicated that the relative abundances of IL4 mRNA and protein were greater in the PBMC of pregnant than non-pregnant cows. Thus, the increase from day 14 to 18 of pregnancy in the concentration of IL4 in the PBMC of pregnant cows could be necessary for pregnancy to occur in cattle (Yang et al., 2018) and IFNT from the conceptus could be the modulator of the increased gene expression.

5. Conclusions and perspectives

During the postpartum period, there are regulated changes in the endocrine status and immune system function that are precisely controlled so as to respond to infections, facilitate uterine involution, and increase the probability of a subsequent pregnancy occurring. Because of the endocrine and immune regulated “crosstalk” between the mother and the conceptus is likely initiated before implantation, the inflammatory mechanisms induced that are related to calving should be elucidated to a greater extent through conducting future studies. Results from these studies would enhance the understanding of how to best manage cows for adaptation to milk production and increase the probability of a subsequent pregnancy occurring. In few studies has there been an assessment of the maternal immune system in relation to lactation and reproductive performance in cattle. In contrast, in several studies there has been an evaluation of the relationship between the immune response during the peripartum period and the nutritional status of animals, as well as the effect of the metabolic milieu on the function of immune cells. Further studies are needed, however, to understand the alterations in function of the immune system in animals when stressful conditions occur such as rapid shifts to large amounts milk production subsequent to parturition, and the possible effects on subsequent fertility. Perhaps, this information will lead to an enhanced understanding of which factors lead to the less-than-desirable pregnancy rates in dairy cows in many circumstances.

Conflict of interest

The authors declare that they have no conflict of interest.

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