IMMUNOLOGICAL STATUS OF THE PUERPERIAL UTERUS IN COW

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Abstract

The reproductive tractus presents a series of innate defending (nonspecific) mechanisms and adaptative (specific) mechanisms, that can be affected by the endocrine status during pregnancy and puerperium. The conceptus grows under correct function of the immune system of the cow. One cytokine in particular, colony-stimulating factor 2, can promote preimplantation development and cause changes in conceptus function that increase the possibilities the conceptus develops to term. The puerperal period is characterized by an increased risk of uterine infections due to anatomic barriers which remain open for a few days. In this case bacteria are detected by the endometrial specialized immune cells which have toll-like receptors for the bacterial liants like peptidoglycans and lipopolysaccharides. The activation toll-like receptors enhances the synthesis and production of pro-inflammatory cytokins like the α tumoral necrosis factor and nitric oxide, which mobilizes the immunitary cells. There are at least 11 types of toll-like receptors which recognize bacterial and viral particles. Toll-like receptor 2 detects the peptidoglycan associated with lipoteichoic acid, lypopeptides and zimoshan, while toll-like receptor 4 and 9 recognize single liants, lipopolysaccharides and unmetilated bacterial DNA. Polimorphonuclear leukocytes (mainly neutrophils), monocytes and circulant macrophages, represent the first line defence against bacteria. Neutrophilic phagocytant activity is initiated by complement system and antibodies. Interleukin 6 appears in the first inflammatory stage, activates mature neutrophils, helps in their maturation, differentiates monocytes in mature macrophages and, also, differentiates natural killer cells. The role of different immunoglobulines (IgA, IgG, IgM) in local defence mechanisms and the endometrial synthesis rate or in other layers of the bovine reproductive tract has not been sufficiently studied yet. Still, some of these immunoglobulins have been identified in the cervico-vaginal secretions of cows infected with Campylobacter fetus. Pre-parturtm period is accompanied by peripheral leucocytosis which is followed by peripheric leucopenia during the first week post-partum.

Key words: cow, immunology, infection, puerperium, reproductive tractus.

INTRODUCTION

The health condition of high-yielding dairy cows is particularly at risk in the transition period, which includes the 3 weeks before and 3 weeks after parturition, broadly corresponding to periparturient period (LeBlanc et al., 2011; Trevisi et al., 2012; Islam et al., 2014). In this season, animals undergo pronounced physiological changes that might cause suppression of the host defence mechanisms including both the cellular and humoral response of the immune system and an increase in susceptibility to uterine and mammary gland infection (Mulligan et al., 2008; Tan et al., 2012). Several factors may influence the degree of immunosuppression at calving, including changes in nutrition, elevations in cortisol levels, and reproductive hormone fluctuations

(Preisler et al., 2000; Stabel et al. 2003). Relaxation of the vulva and cervical dilatation during and after the onset of parturition allows the entry of bacteria into the uterus, causing infection in 80-100% of cows by 14-21 days post-partum (Sheldon et al., 2009; Islam et al., 2013). These bacteria are represented by *Escherichia coli*, *Arcanobacterium pyogenes*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, *Staphylococcus aureus*, *Streptococcus uberis*, *Clostridium* spp., *Prevotella* spp. and *Fusobacterium* spp. (Herath et al., 2006; Singh et al., 2008). The improper balance between uterine infection and the intrauterine antimicrobial self-defence mechanisms often lead to the main post partum reproductive diseases such as puerperal metritis, clinical endometritis, pyometra and subclinical

endometritis (Földi et al., 2006; Sheldon et al., 2008; Islam et al., 2013).

Innate immunity is principally responsible for the elimination of bacterial contamination of the uterus after parturition. This system includes anatomical and physiological barriers to prevent bacterial entry and local cellular defences to neutralise bacteria (particularly phagocytosis of microorganisms by neutrophils), but some infections cannot be eliminated without the active mobilisation of adaptive cellular or humoral immune responses (Sheldon et al., 2008; Sheldon et al., 2009).

BACTERIAL CONTAMINATION OF PUERPERAL UTERUS IN COW

The uterus is often contaminated with bacteria during sexual intercourse or after parturition, causing considerable infertility in humans and animals (Herath et al., 2006; Turner et al., 2012). During parturition, the physical barriers of the cervix, vagina and vulva are compromised providing an opportunity for bacteria to ascend the genital tract from the environment (Herath et al., 2006). Management at calving plays an important role in the subsequent reproductive performance of dairy cows. Susceptible cows are usually those which have high-producing (Galvão et al., 2011) or suffered previously from dystocia, retained placenta (occurs in postpartum cows at a rate of 4-12% in which the foetal placenta was not expelled from uterus until 12 hours after calving) (Ishikawa et al., 2004) twin birth, stillbirth, foetal maceration, primiparity, male offspring, abortion, prolapsed uterus, or metabolic disorder (ketosis and hypocalcemia) (Mulligan et al., 2008; Galvão 2013; Esposito et al., 2014).

Previous studies have reported a relationship between negative energy balance accompanied by elevated ketone levels during early lactation, and periparturient diseases, including showed an association between accumulation of lipids in liver and increased length of bacterial shedding in cows with mastitis (Hammon et al., 2006). A complete list of bacteria can be found in the work by Williams et al. (2005), but mainly *Escherichia coli* (*E. coli*), *Trueperella* (formerly *Arcanobacterium*) *pyogenes* (*T. pyogenes*), *Fusobacterium necrophorum* (*F. necrophorum*),

and *Prevotella melaninogenica* (*P. melaninogenica*) were isolated from cows with metritis (Potter et al., 2010; Galvão 2013; Henriques et al., 2014). These main bacteria are believed to work synergistically increases the risk of clinical endometritis and its severity. In fact, *E. coli* increases the susceptibility of the endometrium to subsequent infection with *T. pyogenes*, and *T. pyogenes* acts synergistically with *F. necrophorum* and *P. melaninogenica* to enhance the severity of uterine disease (Galvão 2013). Puerperal metritis (PM) and clinical endometritis (CE), produced by this bacteria, in herds usually reaches 20–40% and the occurrence of subclinical endometritis is probably even higher (Dolezel et al., 2010; Bicalho et al., 2012). These infections perturb normal ovarian cycles by suppressing follicular growth and disrupting luteolysis. Le Blanc et al. (2006) cited by Bell et al. (2007) and by Krause et al. (2014) indicated that a high proportion of cows have spontaneous resolution of endometritis until at least 4 weeks postpartum (Bell et al., 2007; Krause et al., 2014); the same result was obtained by Esposito et al., (2014).

THE INNATE IMMUNITY DEFENCES OF THE UTERUS

This system is compose by anatomical and physiological barriers preventing bacterial entry and local cellular defences neutralizing bacteria (Turner et al., 2012; Roumegous, 2013). If these barriers cede, the bacteria is detected in cells of the endometrium and immune cells which are tooled with different receptors for the detection of bacterial ligands (Singh et al., 2008; Turner et al., 2012).

ANATOMICAL, PHYSIOLOGICAL AND CHEMICALL BARRIERS

The genital tract, including the cervix, usually offers an effective barrier against the entry of pathogens. The vulva is the first line of defence against faecal contamination. The vestibule (with its sphincter) and the cervix are composed of rigid rings and cartilage mucous folds allow a quasi seal system. The circular and longitudinal uterine muscular layers promote physical expulsion of bacteria trapped in mucus deriving endometrial glands (Singh et al., 2008;

Roumegous, 2013). Also, the endometrium is an anatomical barrier which is covered by simple or pseudostratified columnar epithelium (Azawi, 2008). However, the genital tract undergoing a major expansion, which then compromises their barrier function: in fact, 96 hours after calving, cervical dilatation still allows the passage of two fingers (Singh et al., 2008; Roumegous, 2013). Epithelial cells are the first to make contact with potential pathogens that enter the uterus. Epithelial and stromal cells interactions are critically important for endometrial function, with stromal cells affecting epithelial cells through both the release of soluble factors and turns over of extra cellular matrix (Wira et al., 2010).

THE PHAGOCYTOSIS AND THE CELLS INVOLVED IN THIS PROCESS

First line of defence against bacteria is represented by neutrophils, blood monocytes and macrophages (Tan et al., 2012). Elimination of bacterial infections through phagocytosis involves recruitment of neutrophils from the circulation and bone marrow by chemotaxis to sites of infection (Singh et al., 2008; Roumegous, 2013). This influx of neutrophils and their diapedesis into the uterine lumen are favoured by several factors: the power exerted chemotactic cytokines released by the endometrium, uterine vasodilation in response to IL-1, and the increase in vascular permeability as a result of mast cell degranulation products (Roumegous, 2013). The phagocytic activity of neutrophils is enhanced by the serum complement system and by antibodies (Singh et al., 2008). The neutrophils are bear on by pre-partum peak of glucocorticoids determines a neutrophilia, followed by a neutropenia, due to the migration of neutrophils to the uterus and mammary gland (Silva et al., 2008). Neutrophil function is decreased around the time of calving (15 days prepartum) and in puerperium (30 days post calving) in high-producing dairy cows, especially in those that develop uterine disease (Galvão et al., 2011; Islam et al., 2013).
The uterine activity of phagocytosis can be attributed to the 80% neutrophils and 20% macrophages (Roumegous, 2013). Phagocytosis induced phenomenon that can be done in two different ways, depending on the resistance of the bacteria: first, without opsonization (then there is a direct interaction between the receptor on the surface of phagocytes and antigen), and second, with opsonization (interaction require an additional molecule, opsonin, which then plays the role of adapter between the bacterium and the leukocyte) (Roumegous, 2013). Then the phagocytosis continues with a step of adhesion, and then a phase in which the pseudopodia surrounding the bacteria are then called phagosome form a vacuole (Roumegous, 2013). Finally a phase of destruction allows complete digestion of bacteria. Shortly, activation of these cells results in adherence, attachment, ingestion and digestion of invading bacteria (Singh et al., 2008).

THE ADAPTIVE IMMUNITY DEFENCES OF THE UTERUS.
HUMORAL IMMUNITY

Humoral immunity is provided by circulating specific antigen molecules named immunoglobulins (Ig), produced by locally plasmocytes who derived from B lymphocytes (Roumegous, 2013). These immunoglobulins are responsible for neutralizing the bacteria directly on the uterine lining. Albeit antibody-secreting cells are present in the bovine uterus, their contribution to local immunity by the local synthesis of specific antibodies is not known (Singh et al., 2008). Immunoglobulin (Ig) classes A, G and M were identified in genital secretions of the cow and reflect endometrial inflammation following bacterial contamination. Intrauterine inoculation of *Trueperella pyogenes* causes the increase of specific immunoglobulins in uterine secretions (Roumegous, 2013). Another example is provided by Singh et al. (2008), who cited some studies about cattle immunized with *Campylobacter fetus* subsp. *venerealis, A. pyogenes* or *Histophilus somni* (*Haemophilus somnus*); he reported specific antibodies in the uterine and cervico-vaginal secretions of the cow (Singh et al., 2008). Immunoglobulins act either by lysing the bacteria directly, or by opsonizing to facilitate phagocytosis, or by activating the complement system in the uterine lumen (Singh

et al., 2008; Silva et al., 2008; Roumegous, 2013).

If presence of all other major immunoglobulins in bovine endometrial secretions is regarded as a reflection of an endometrial inflammatory process after bacterial challenge and clinical recovery, the Ig E represented the exception. Ig G predominated in the uterine lumen so that Ig A is predominant in the posterior part of the genital tract of the cow (upmost the vagina) (Herath et al., 2006; Singh et al., 2008; Silva et al., 2008; Roumegous, 2013). The main mode of action of secretory IgA is the inhibition or neutralization of bacterial adhesion to the epithelium without other inflammatory phenomena occur. The production of Ig G from two sites: one fraction is synthesized locally in the endometrium (Ig G_1) while the other part comes to the transudation of serum-peripheral circulation (Ig G_2). IgG bind and activate the complement system (Singh et al., 2008; Roumegous, 2013). The type of Ig G species produced in the genital tract may also depend on the nature of the stimulating antigens. For example, infection with *Tritrichomonas fetus* is characterised by a T helper (Th) 2 type response and production of IL4 and IgG_1, while infection with *Brucella abortus* stimulates Th1 responses, characterised by the production of IgG_2, IFNγ and cytotoxic $CD8^+$ T lymphocytes (Ishikawa et al., 2004; Singh et al., 2008). Ig G may also opsonize bacteria for phagocytosis by neutrophils and macrophages. Their importance to the surface of the uterine plasma and genital secretions suggests that this class of immunoglobulin is very important for the defense of the genital tract of the cow (Singh et al., 2008; Roumegous, 2013). IgM immunoglobulins are synthesized as early and effective for agglutination and activation of the complement system, responsible for the lysis of pathogenic. Briefly, immunoglobulins act mainly directly lysing the bacteria, but also indirectly by participating in the opsonization and phagocytosis stimulation (innate immunity) (Roumegous, 2013).

THE ACTIVATION OF CELL-MEDIATED IMMUNITY

During mid- and late pregnancy, lymphocytes and macrophages are found in the inter-caruncular endometrium, but not in the caruncular endometrium, indicating that the immune response is both local and specific to the areas adjacent to fetal tissues or foreign antigens (Singh et al., 2008; Sheldon et al., 2009). An excellent marker of lymphoid aggregates in bovine in healthy endometrium previously was integrin subunit α4, a transmembrane glycoprotein that exist in close association with the cytoskeleton and signaling proteins (Kimmins and MacLaren, 1999).

The subepithelial uterine stroma is largely drained by a lymph network and there is infiltrated of plasma cells (Th, B lymphocytes), antigen-presenting macrophages (CD14+ cells), and mast cells compared with other regions of the endometrium and the myometrium (Sheldon et al., 2009). Also, the peak in CD 14+ cell numbers was coincidental with the cortisol peak concentrations (Silva et al., 2008). Mast cells have a prominent sensor and effector function during bacterial infections in mammals, but their role in response to intrauterine bacterial contamination in cattle is not clear (Sheldon et al., 2009).

There are two main types of T lymphocytes. First one is represented by CD8+ T lymphocyte or cytotoxic T-cells which recognize an antigen carried by a molecule of the major histocompatibility complex (MHC) type I (Hansen, 2011). They typically differentiate into cytotoxic lymphocytes and produce relatively few cytokines. Second one is the CD4+ T lymphocytes or T-helper cells that recognize an antigen carried by a molecule of CMH type II. Their main action is the release of cytokines (IL-2), which amplify and direct the immune response, hence the term given to the helper T cell. We differentiate two types of CD4+: guiding the helper lymphocytes to a cytotoxic response (Th1) and those directed towards a humoral (Th2) (Singh et al., 2008; Roumegous, 2013). The percentage of CD+4 T cells from healthy adult cattle is approximately 25-35% (Karcher et al., 2008). T helper lymphocytes are about twice as many in the superficial stromal layer (stratum compactum) in the deep layer (stratum spongiosum) and predominate around the ducts of the uterine glands (Roumegous, 2013). The population of endometrial cells varies during different stages of gestation. For example, the percentage of T

lymphocytes in the peripheral circulation changed from 45% during mid-lactation to 20% in periparturient cows (Singh et al., 2008). And their concentration increases during late gestation in intercaronculaires areas, indicating a function of recognition and protection against antigens that penetrate the uterus (Singh et al., 2008; Roumegous, 2013). Uterine cellular immunity is based on cytotoxic T lymphocytes (Roumegous, 2013).

The CD4+ to CD8+ ratio is often used as an indicator of immune status. Subclinically infected cows had lower CD4:CD8 ratios, whereas the clinically infected cows had higher CD4+:CD8+ during the immediate postpartum period (Karcher et al., 2008).

THE COMPLEMENT SYSTEM (CMH)

The CMH is formed by a complex of soluble proteins and activating in two moods: classical complement pathway targets antigen-antibody complexes, and alternative pathway targets foreign surface antigens. The activation of these two pathways lead to the formation of C3 convertase, followed by formation of a membrane attack complex and lysis of target cells (Singh et al., 2008). The presence of all serum complement proteins in bovine uterine secretions is not thoroughly documented, but physiological haemorrhage from the caruncular endometrium during parturition is likely to bring cellular and serum components, including complement, to the uterine lumen. Degranulation of uterine mast cells releases tryptase and other proteases that can activate complement components C3 and C5 to generate anaphylatoxins (Küther et al., 1998; Singh et al., 2008).

PATHOGEN-ASSOCIATED MOLECULAR PATTERNS

The presence of invading microbes and the resulting tissue damage is detected by "sentinel cells" (macrophages, dendritic cells and mast cells) (Tizard, 2004). Following pathogen recognition, immune cells release pro-inflammatory molecules including tumour necrosis factor-α (TNFα), interleukins (IL-1, IL-6, IL-8, IL-12) and nitric oxide (Ishikawa et al., 2004). These molecules aid the recruitment and activation of more immune cells and stimulate hepatic secretion of acute phase proteins. Thus, it is not surprising that peripheral plasma acute phase protein concentrations increase around the time of parturition in cattle, and then decrease with the concomitant elimination of bacterial contamination and uterine involution (Herath et al., 2006).

Most pathogen-associated molecular patterns (PAMPs) are evolutionary conserved molecules like cell wall components and nucleic acids that are required for the function of microbes. Bacterial cell wall components are the most clearly characterized PAMPs and probably the most important in the endometrium. The most obvious distinguishing feature of Gram-negative bacteria is the presence of lipopolysaccharides (LPS) in the outer membrane of the bacterial cell wall with important roles in the integrity and physiological function of the wall. Also, the cell walls of Gram-positive organisms are largely composed of peptidoglycans and lipoteichoic acid and acid-fast bacteria are covered in glycolipids (Tan et al., 2012; Turner et al., 2012).

The main families of pattern recognition receptors (PRR) are Toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) and C-type lectin receptors (CLRs) (Turner et al., 2012).

TOLL-LIKE RECEPTORS (TLRs)

These receptors are expressed on macrophages and mast cells, as well as on dendritic cells, eosinophils, and epithelial cells representing the principal PAMPs belongs mammals (Beutler et al., 2003; Tizard, 2004). There are at least 11 of these TLRs, which detect most bacteria and viruses. The best characterized member of the TLR family is TLR4, which is widely expressed by hematopoietic and non-hematopoietic cells, and recognizes LPS of *E.coli* and pyolysine of *Trueperella pyogenes* (Roumegous, 2013), in complex with two co-receptors, CD14 and MD-2 (Singh et al., 2008; Sheldon et al., 2009; Loyi et al., 2013). Heterodimers of TLR2 /TLR1 or TLR2/TLR6 recognize a variety of PAMPs from both Gram-positive and Gram-negative bacteria

including lipopeptides and peptidoglycan, glycolipids and lipoteichoic acid. The receptor dimerization is important, and tri-acetylatedlipopeptides are usually bound by TLR2/TLR1 whereas di-acetylated lipopeptides are bound by TLR2/TLR6. Bacterial flagellin is recognized by TLR5. TLR2 could recognize LPS from Gram-negative bacteria such as *Porphyromonas gingivalis*, *Helicobacter pyroli* and non-enterobacteria (Fu et al., 2013). Doublestranded RNA (dsRNA) from viruses is bound by TLR3, although a synthetic analogue (polyinosinedeoxycytidylic acid) is widely used in vitro to examine TLR3 activity. Uridine or guanosine-rich single-stranded RNAs from a variety of viruses and synthetic imidazoquinoline-like molecules such as resiquimod are recognized by TLR7 and TLR8. Finally, TLR9 recognizes the unmethylated CpG motifs of single-stranded DNA present in the genomes of many viruses and bacteria (Herath et al., 2006; Davies et al., 2008), but the ligand for TLR10 is still not known (Davies et al., 2008). Before and after parturition, TLR2, TLR3, TLR4, TLR6, and TLR9 are expressed in the caruncular and intercaruncular endometrium, and TLR expression was greater in the caruncular endometrium than in the intercaruncular endometrium 4–6 h postpartum (Sheldon et al., 2009).

OTHER PRRs INVOLVED IN IMMUNITY

The NLRs first identified were nucleotide oligomerization domain NOD1 and NOD2, which recognize components of peptidoglycan: NOD1 recognizes D-c-glutamyl-meso-DAP dipeptide found in all Gram-negative but only some Gram-positive peptidoglycans, whereas NOD2 recognizes the conserved muramyl dipeptide motif found in all PGNs.

The RIG-I receptor is involved in the recognition of Paramyxoviridae, Filoviridae and Rhabdovirdae among others, whereas MDA5 is important in the recognition of Picornaviridae. The role of these RIG-I receptors in uterine disease of domestic animals is mostly unexplored but warrants attention because viruses such as bovine viral diarrhea (BVD) virus and bovine herpesvirus 4 (BoHV-4) cause infertility and abortion. Indeed, bovine herpesvirus 4 is tropic for the bovine endometrial stromal cells where it drives the activation of the gene promoter for thechemokine IL-8 (Donofrio et al., 2010; Turner et al., 2012).

Cellular CLRs include dectin-1, dectin-2, and the mannose receptor. Dectin-1 recognizes specific glucose polymers found in the cell walls of fungi including *Candida albicans* and *Saccharomyces cerevisiae* (Turner et al., 2012).

CYTOKINES

When exposed to infections agents or their PAMPs, the sentinel cells, embryo, peripheral blood lymphocytes, oviductal and endometrial cells secrete many different molecules. These molecules include the major cytokines interleukin-1 (IL-1) and tumor necrosis factor-α (TNF- α), as well as others, such as IL-6, IL-12 and IL-18 (Gruys et al., 2005; Roumegous, 2013). They also secrete oxidants, such as O_2^-, H_2O_2, OH, and NO, and lipids, such as the lukotrienes and prostaglandins (Tizard, 2004).

Cytokines acting as messengers between the local site of injury and the hepatocytes synthesising the acute phase proteins. The serum concentration cytokines increases within a few hours after the initiating stimulus and then is usually cleared from the circulation within a few hours (Petersen et al., 2004; Roumegous, 2013).

Second line acute phase proteins (such as heptaglobin and serum amyloid A) (Petersen et al., 2004; Davies et al., 2008) are induced primarily by IL-6 type cytokines and are characterised by a later increase in serum concentration remaining elevated for up to two weeks (Petersen et al., 2004; Roumegous, 2013). It has been reported that IL-1, TNFα and IL-6, are secreted within the cervix at parturition (Engelen, 2008).

Next to interleukins 1β, 6 and 8, TNF-α it suppose that chemokine, prostaglandin-endoperoxide synthase 2 (PTGS2), and haptoglobin are involved in physiological events in the bovine endometrium. Real-time RT-PCR has revealed that CXCL5, IL1B, IL8 and TNF mRNA are significantly higher expressed in the endometrium of cows with subclinical or clinical endometritis than in healthy cows (Gabler et al., 2010; Wira et al., 2010).

A recently published study describes the expression of several pro-inflammatory cytokines including IL1α, IL1β and IL6 in the first week postpartum in endometrial biopsies (Gabler et al., 2010).

Bovine herpesvirus 4 is tropic for the endometrium and the only virus consistently associated with postpartum metritis. The chemokine IL8 plays a central role for granulocyte trafficking, particularly for attracting neutrophils into the bovine uterus (Engelen, 2008; Donofrio et al., 2010; Galvão et al., 2011). It was hypothesized that IL-8 would be decreased early in lactation and increased later in lactation in cows that develop endometritis (Galvão et al., 2011). IL1 increases the plasma calcium concentration, which stimulates myometrial contractions and the removal of debris from the uterus and it is hypothesized that IL-1 may be increased in the cows suffering from postpartum reproductive diseases (Islam et al., 2013). Islam et al. (2013), observed significantly lower IL-1 in the normal cows at 30 days postpartum (Islam et al., 2013). High levels of IL6 were associated with bovine endometritis, while low levels were associated with retention of the placenta (Singh et al., 2008).

CONCLUSIONS

After a normal calving, most of the bacteria are eliminated spontaneously until at least 4 weeks postpartum. Following normal parturition, the phagocytic capacity of bovine neutrophils remains high throughout the peripartum period, but the killing capacity and oxidative burst activity of neutrophils is decreasing. These activities are enhanced 1 week after parturition, which favours the spontaneous resolution of uterine infection.

Other cellular components, including lymphocytes, eosinophils, mast cells and macrophages, are also mobilised and activated in the uterus during the post-partum period.

TLR4 receptors present on bovine endometrial cells initiate a signalling cascade stimulating the production of TNFα, IL-1 and nitric oxide, which orchestrate immune response that are involved in clearance of infection. Also it was observed that CD4+ to CD8+ ratio is often used as an indicator of immune status. We can conclude that chemokine IL8 plays a central role for granulocyte trafficking, particularly for attracting neutrophils into the bovine uterus $PGF_{2α}$ is a pro-inflammatory molecule that stimulates the production of cytokines that enhance phagocytosis and lymphocyte function.

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