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Application of Acute Phase Proteins for Monitoring Inflammatory States in Cattle

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1. Introduction

The animal body functions in a controlled internal environment, strictly regulated by a variety of homeostatic mechanisms. However, the internal milieu is disturbed by external factors that lead to imbalance of the inner homeostasis. The host is equipped with multiple tools to abolish external challenges like tissue injury and infection by activation of various defense mechanisms; however, mobilization of all these responses is associated with alterations of the homeostatic status. The multifaceted immune and metabolic responses of the host to external challenges are commonly referred to as the acute-phase response (APR) (Kushner, 1982; Koj, 1985; Baumann & Gauldie, 1994; Moshage, 1997; Mackiewicz, 1997). The aim of the APR is to eliminate the agent(s) that caused the interference and to bring the homeostasis back to normality (Figure 1). The APR is initiated in response to a variety of stimuli including acute trauma, bacterial infection, surgery, fracture, burns, tissue necrosis, presence of a chronic disease, or ongoing inflammatory processes (Kushner, 1982; Gordon & Koj, 1985; Baumann & Gauldie, 1994; Steel & Whitehead, 1994; Boosalis et al., 1996; Mackiewicz, 1997). The APR usually resolves within a few days or weeks, however sometimes it can persist when the causal agent is defiant (Boosalis et al., 1996; Mackiewicz, 1997; Koj, 1998).

The APR is regulated by numerous compounds referred to as cytokines (Mackiewicz, 1997; Koj, 1998; Martin et al., 1999). The latter are produced by macrophages, when they are activated by bacterial endotoxin, viruses, free radicals, prostaglandins, or other factors released under different inflammatory conditions. The main cytokines released by macrophages are interleukin-1 (IL-1), IL-8, tumor necrosis factor-alpha (TNF- α), and interferon-gamma (INF- γ) (Koj, 1998; Martin et al., 1999). The release of proinflammatory cytokines, at the site of tissue injury, stimulates various other cell types to produce a cascade of other cytokines, including IL-6-type cytokines, which act to stimulate the production of acute phase proteins (APP) from liver hepatocytes or other tissues (Baigrie et al., 1991; Mackiewicz, 1997). Although the production of cytokines in the liver or other local sites is complex, it is believed that IL-1 and IL-6 are the two main stimulants of APP production (Gauldie et al., 1987; Nijsten et al., 1991; Ohzato et al., 1992).

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Over the years three different systems of classification of APP have been developed. The first system is based on the degree of blood elevation of the APP, referred to as positive or negative APP; the second system is based on the time when APP are released during an APR; and the third system is based on the subset of cytokines responsible for stimulating gene expression of APP (Mackiewicz, 1997; Moshage, 1997). In the first system, positive APP are classified into one of three groups based upon the degree of rise in the blood concentration: type I APP, whose concentration increases by 50% (e.g. ceruloplasmin (Cp), complement factor C3, and factor C4); type II APP, whose concentration increases 2- to 5-fold (e.g. fibrinogen and haptoglobin - Hp); and type III APP, whose quantity rises more than 5-fold the normal value [e.g. C-reactive protein (CRP) and serum amyloid A (SAA)]

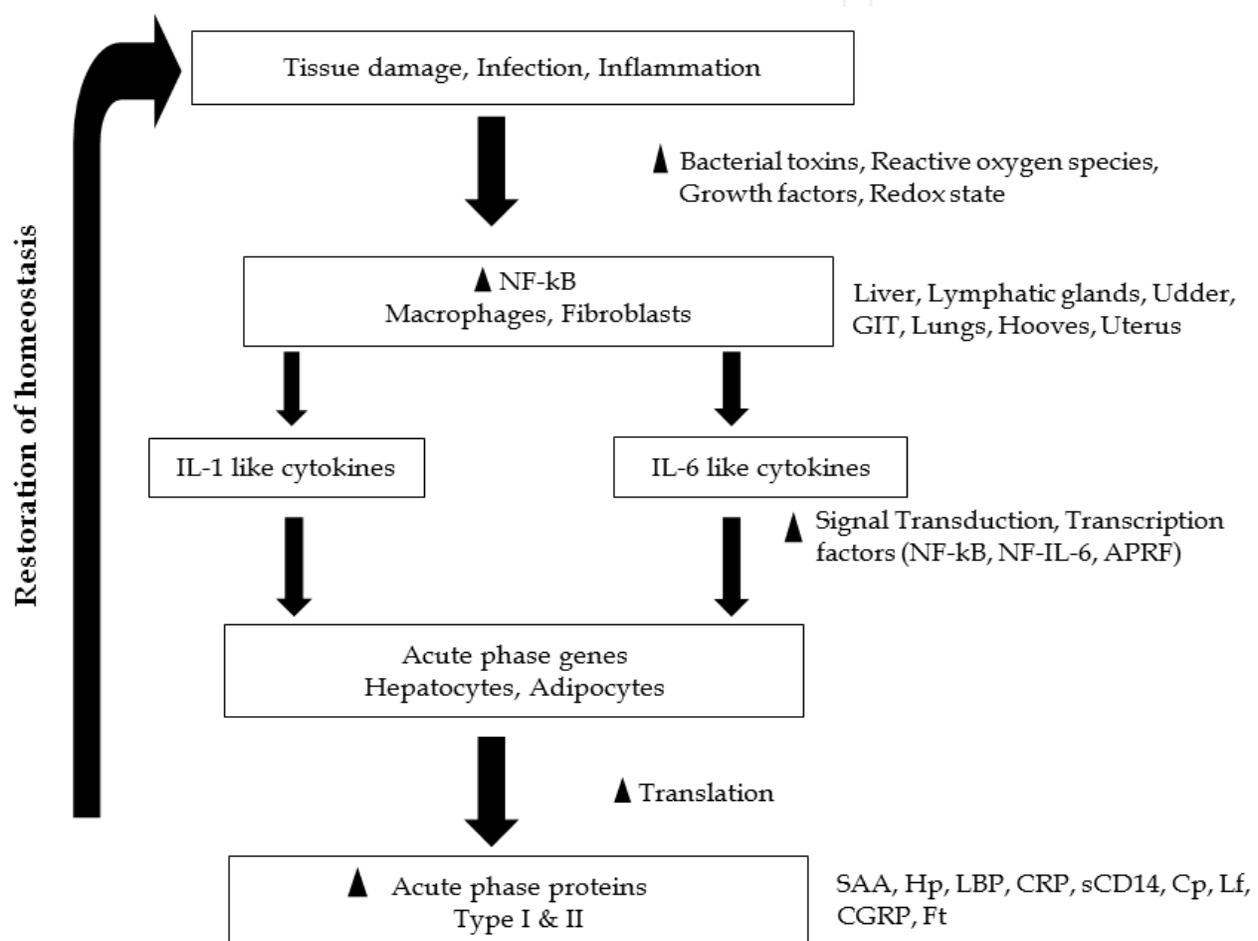


Fig. 1. Acute phase response in animals triggered by infection, tissue damage or inflammation initiates rapid activation of transcription factor NF-kB in macrophages and fibroblasts in peripheral tissues. This is followed by increased production of cytokines. Subsequent signaling cascades result in transcription of acute phase genes and ultimately, secretion of acute phase proteins that function to restore homeostasis. APRF: Acute phase protein factor; CGRP: Calcitonin gene related peptide; Cp: Ceruloplasmin; CRP: C-Reactive protein; Ft: Ferritin; Hp: Haptoglobin; IL: Interleukin; Lf: Lactoferrin; LBP: Lipopolysaccharide binding protein; SAA: Serum amyloid A; sCD14: Soluble cluster of differentiation antigen 14.

(Mackiewicz, 1997; Moshage, 1997). A few APP decrease during an APR and they are known as negative APP. The most studied negative APP include retinol binding protein (RBP), albumin, transferrin, and transthyretin.

Based on the time when they are released APP are classified as either first- or second-phase proteins (Kushner & Mackiewicz, 1987; Mackiewicz, 1997). Examples of the first-phase APP are SAA and CRP, whose levels rise as early as 4 h after the initiation of inflammation, peak within 1-3 d, and quickly return to baseline concentrations (Mackiewicz, 1997). Examples of the second-phase APP are Hp and fibrinogen, which increase 1-3 d after the initiation of APR, peak within 7-10 d, and decrease to baseline levels within 2 or more wk (Mackiewicz, 1997; Moshage, 1997).

The third system classifies APP based on which cytokine subsets induce their gene expression (Baumann & Gauldie, 1994; Mackiewicz, 1997). Type I APP are induced by IL-1-like cytokines, including IL-1 α , IL-1 β , TNF- α , and TNF- β , and synergistically by IL-6-like cytokines, while type II APP are stimulated by IL-6-like cytokines alone, including IL-6 and IL-11 (Baumann & Gauldie, 1994; Mackiewicz, 1997; Moshage, 1997). C-reactive protein, SAA, and C3 are examples of type I proteins, while type II proteins include Hp and fibrinogen.

At least forty different plasma proteins have been defined as APP. They include clotting proteins, complement factors, anti-proteases, and transport proteins (Samols, 2002). However, the number of APP commonly used in cattle research is smaller than in human research. In this chapter we will discuss only about 9 of the most studied APP in cattle.

Recent evidence also indicates that several APP are secreted extrahepatically playing important roles in immune defenses against different pathogens populating mucosal layers in the body. In the following sections we will discuss the most recent reports regarding structures, functions, tissue expression as well as various factors that affect expression and production of SAA, Hp, LBP, soluble(s)CD14, CRP, Cp, lactoferrin (Lt), calcitonin gene-related peptide (CGRP), and ferritin in cattle (i.e., dairy and beef cattle).

2. Serum amyloid A

2.1 Structure

Serum amyloid A is an APP that belongs to a family of apolipoproteins that are coded by different genes with a high degree of homology between species (Uhlar, 1994; Malle, 1993). The family of SAA proteins in mammals has a MW of 12 kDa with 104 amino acids. They are very well conserved throughout evolution and have a wide range of functions.

2.2 Functions

It is known that SAA is over expressed several orders of magnitude during infections and inflammation. Four different isoforms of SAA have been described in humans and mice (Uhlar & Whitehead, 1999) and seven different isoforms were reported in the blood of dairy cows (Takahashi, 2009). Among the known isoforms, SAA1 and SAA2 are the only ones reported to be overproduced during the APR and are known as acute phase (A)-SAA. They are mainly expressed in the liver hepatocytes. The third isoform, SAA3, is expressed extrahepatically by adipose tissue, mammary gland, intestinal epithelial cells, and macrophages and is present in the plasma at a very low level (Meek, 1992; Chiba, 2009; Eckhardt, 2010). The fourth isoform, SAA4, is constitutively expressed (de Beer, 1995) and does not respond to external stimuli. A recent investigation in cows with amyloidosis and chronic inflammation showed seven different isoforms of SAA in the serum (Takahashi,

2009). Larson (2005) reported production of SAA3 by ductal cells in the mammary gland of healthy lactating dairy cows. Moreover, Mukesh (2010) showed presence of SAA3 in the adipose tissue of dairy cows. However, the precise functions of these seven different isoforms of SAA in dairy cows are not known yet.

Serum amyloid A is transported in blood in association with lipoprotein particles, particularly high-density lipoproteins (HDL) (Eriksen, 1980; Coetzee, 1986). During an APR, SAA replaces almost 85% of the apolipoprotein-A1 (apo-A1) and becomes the main apolipoprotein on HDL (Uhlir & Whitehead, 1999; Coetzee, 1986). The reason for replacement of apo-A1 during APR is related to the fact that SAA half-life is 75-80 min compared with that of apo-A1 of 11 h (Hoffman & Benditt, 1983). It is believed that endotoxin-lipoprotein complexes are quickly removed from circulation by liver hepatocytes (Harris, 2002; Ametaj, 2010). The shorter half-life of SAA might help in expedited clearance of endotoxin-lipoprotein complexes from circulation (Harris et al., 1998).

The main known functions of SAA are to: 1) bind to lipoproteins and help in their expedited clearance from liver hepatocytes (Harris, 2002), 2) extract cholesterol from cells (van der Westhuyzen, 2007); 3) bind and activate neutrophils and macrophages (Furlaneto & Campa, 2000), 4) kill coliform bacteria (Shah, 2006). Other reported functions of SAA include suppression of lymphocyte response to antigens (Benson, 1979), inhibition of platelet aggregation (Zimlichman, 1990), and regulation of expression of tissue collagenase (Brinckerhoff, 1989). In addition, SAA has been shown to stimulate adhesion of mast cells to the extracellular matrix (Hershkovich, 1997), migration and adhesion of T cells (Preciado-Patt, 1996), and migration, adhesion, and tissue infiltration of monocytes and neutrophils (Badolato et al., 1994). Serum amyloid A also induces mobilization of calcium (Ca) and chemotaxis in monocytes (Badolato, 1995) and enhances synthesis of eicosanoid in human monocytes (Malle, 1997).

Although early research indicated that SAA in dairy cows is increased more during acute rather than chronic inflammatory conditions (Horadagoda, 1999), recent research shows that SAA is also increased during chronic conditions (Chan, 2010). This protein is also raised following experimental infection of cattle with *Mannheimia haemolytica* and during bovine respiratory syncytial virus infections (Horadagoda, 1994; Heegaard, 2000).

2.3 Factors that affect its expression

2.3.1 Mammary gland infections

Molenaar (2009) demonstrated presence of a constitutive isoform of SAA3 in the mammary gland tissue of dairy cows. These authors reported that the expression profile of SAA3 was different in relation with stage of lactation and disease. Thus, SAA3 was high in the mammary tissue of pregnant cows, low during lactation, elevated during involution of the gland, and strongly increased during mastitis. An interesting observation of the same authors was that SAA3 was not expressed in lactational tissues of the gland (i.e., alveoli) but only in the epithelial cells lining ductal tissue of the teat. The role of SAA3 in ductal cells might be to protect the teat potential colonization of that area by bacteria during milking or suckling. Several other authors have reported elevated mammary gland SAA3 in the milk of cows and ewes with mastitis (Eckersall, 2001; Winter et al., 2003; Nielsen et al., 2004; Jacobsen et al., 2005). Moreover, experimental models of mastitis have demonstrated that SAA3 in the mammary gland is synthesized by the infected udder and is not coming from the blood (Grönlund, 2003; Eckersall, 2006). Gram-negative bacterial lipopolysaccharide (LPS) and the Gram-positive bacterial lipoteichoic acid (LTA) were shown to upregulate SAA3 in bovine mammary epithelial cells by 18.5-fold and 12.5-fold, respectively (Larson,

2006). Concentrations of SAA in the milk of normal cows were 0.5 ± 1.0 mg/mL and in cows affected by mastitis were 2.2 ± 8.6 mg/mL (Åkerstedt, 2011). Another group of investigators showed that concentrations of SAA in the serum of normal cows were 3.6-11.0 mg/mL, in those with mild mastitis 5.4-142 mg/mL, and those with moderate mastitis 5.9-141 mg/mL (Eckersall, 2001).

Molenaar (2009) tested the bacterial activity of recombinant SAA3 from the mammary gland and they reported that mammary(M)-SAA3 had antimicrobial activity against *Escherichia coli*, *Streptococcus uberis*, and *Pseudomonas aeruginosa* with the greatest activity against *E. coli*. This offers an explanation as to why the protein is expressed in the mammary gland at times where defense against bacteria is required. Another interesting report comes from Weber (2006) who showed presence of SAA3 in high concentrations in the colostrum of healthy cows. Moreover, the same authors reported that the colostrum SAA3 has a unique four amino acid motif (TFLK) within the first residues that is not present in the isoforms produced in the liver (McDonald, 2001). This isoform has the ability to stimulate intestinal epithelial cells to produce a protective intestinal mucin and lower the adherence of enteropathogenic *E. coli* to these cells (Mack, 2003; Larson, 2003). This feature of SAA3 might help protect newborn calves during their first days of life from enteropathogenic bacteria.

2.3.2 Dietary factors

Recent research work conducted by our team and others has shown that feeding of high grain diets is associated with enhanced concentrations of SAA in the blood of both dairy (Emmanuel, 2008) and beef cattle (Ametaj, 2009). Dairy cows fed barley grain at 0-15% of the diet dry matter (DM) had plasma SAA concentrations between 2-12 mg/mL and those fed 30-45% of diet DM had values ranging between 19-46 mg/mL (Emmanuel, 2008). The reason for the increased SAA in the plasma of cattle fed high grain diets is suggested to be related to translocation of endotoxin into the systemic circulation which then stimulates the release of pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6 by liver macrophages (Gabay & Kushner, 1999), resulting in enhanced secretion of SAA from hepatocytes (Emmanuel, 2008). Our team also showed that feeding high grain diets was associated with development of fatty liver and greater concentrations of SAA in the blood of cows diagnosed with fatty liver. We proposed a role for expedited internalization of SAA-LPS-lipoprotein complexes from liver hepatocytes in development of fatty liver (Ametaj, 2005a; 2005b). Other investigators demonstrated that plasma SAA was increased in cows affected by displaced abomasum (Guzelbektes, 2010).

In another study conducted by our team we found that concentrations of SAA in the plasma of steers, during a 12-wk period of feeding a backgrounding diet with 45% barley grain-based concentrate and 55% barley silage (DM basis), were 2.5-14 mg/mL (Ametaj, 2009). In addition, during a 15-wk period of feeding a finishing diet with 91% barley grain-based concentrate and 9% barley silage concentrations of SAA in the plasma were 8-24 mg/mL (Ametaj, 2009). Plasma SAA was greater in the group of steers fed the finishing diet compared to those fed the backgrounding diet (8.0 vs 17.0 mg/mL). Interestingly, the peak concentration of SAA in steers fed the finishing diet reached at 3 wk (21 mg/mL) after the starting of the diet (Ametaj, 2009).

2.3.3 Uterine infections

Serum amyloid A is related to infections of the uterus in postpartal dairy cows (Chan, 2010). The latter authors indicated that concentrations of SAA in the serum of cows affected by

metritis reached peak values 4-7 d after calving (85 ± 23 mg/mL) compared to healthy cows (48 ± 20 mg/mL) and remained above the baseline values for 2 mo after parturition. This is the first report indicating that SAA might be produced not only during acute states of inflammation but also during chronic diseases such as metritis. Besides its role as an antibacterial compound SAA in the uterus might also activate macrophages and neutrophils to clear the tissue from bacterial infections.

2.3.4 Lameness

Lameness and hoof health is an important disease of dairy cows that affects their wellbeing and most importantly the economic efficiency of dairy farms. In a recent trial several cows were selected on the day they showed signs of lameness and if they were diagnosed with sole ulcers and/or white line abscesses. Concentrations of SAA were reported to be greater in lame dairy cows (37-60 mg/mL) than their counterparts (10-12 mg/mL) during days 0, 4, 7, and 8 of the disease (Kujala, 2010). Serum amyloid A fell on day 14, which was confirmed by healing of cows on that day. Concentration of SAA in the serum of lame cows reached values of 50 mg/mL versus lower than 10 mg/mL of the healthy cows.

2.3.5 Fatty liver and downer cow syndrome

In an investigation about the etiology and pathology of fatty liver we reported that postpartal cows affected by fatty liver had greater plasma SAA compared to the healthy ones (Ametaj et al., 2005a, 2005b). Concentration of SAA in the bloodstream of cows affected by fatty liver reached peak value of ca. 80 μ g/mL (Ametaj et al., 2005a). Moreover, the average concentrations of plasma SAA in cows with fatty liver were greater than those in the control cows during days 3, 8, 12, and 27 postpartum. In the same study, we reported that after 12 d postpartum, mean plasma SAA in fatty-liver cows decreased below prepartal values, and was similar to values for control cows, ca 15 μ g/mL (Ametaj et al., 2005a).

In a case study with clinical signs of downer cow syndrome we also found that plasma concentrations of SAA were between 3.3-11.5 mg/mL during day -14 and -7 before calving, respectively; they increased to 82.7 mg/mL 2 wk after calving and ranged between 11.7-27.8 mg/mL in eight normal cows. These data suggest a role of inflammation and endotoxin in the etiology and pathogenesis of the downer cow (Ametaj, 2010). Although the pathology of this disease has been a mystery for a long time, in dairy industry, the data generated from our team implicate bacterial components or proinflammatory cytokines released in response to these by-products in development of the disease. Further research would be needed to explore the role of inflammatory conditions in etiopathology of downer cows.

2.3.6 Adipose tissue

Both bovine and non-ruminant research has indicated expression of SAA3 in adipose tissue (Poitou, 2009; Mukesh, 2010). The latter authors showed that SAA3 mRNA abundance was greater in mesenteric than subcutaneous tissue of dairy cows. Expression of SAA3 has been related to gastrointestinal bacterial components such as LPS. Moreover, injection of LPS in the mammary gland or intraperitoneum was associated with enhanced SAA3 mRNA in both dairy cows and rodents (Mukesh, 2010). Data with mice support a role for SAA3 in exerting local inflammatory functions in adipose tissue from obese animals (Larson, 2006). The greater abundance of SAA3 mRNA in adipose tissue during an inflammatory challenge could play a role in lipid/steroid metabolism and/or transport (Benditt, 1989). Yang (2006)

suggests that SAA has a long-term effect in stimulating basal lipolysis and that the lipolytic activity of SAA can be an autocrine feedback mechanism by which increased SAA production from enlarged adipocytes limits further triacylglycerol accumulation and increases non-esterified fatty acid (NEFA). The resulting increased release of NEFA into the circulation may contribute to insulin resistance.

2.4 Age-related changes

Alsemgeest et al. (1994) reported that SAA is present in neonatal veal calves and that serum SAA was greater in calves with different inflammatory diseases including diarrhea, pneumonia, and omphalitis. The same authors showed that concentrations of SAA in newborn calves were lower than in adult cows. Weaning and transportation was shown to affect concentrations of SAA in the serum of newly weaned beef calves (Arthington, 2003). Serum SAA were greater on d 1 and decreased steadily on d 3 and 7 (51.2, 43.8, and 28.5 µg/mL, respectively) after transportation.

3. Haptoglobin

3.1 Structure

Haptoglobin (Hp) is another APP reported to be present in the blood of all mammals analyzed so far (Bowman & Kurosky 1982). The protein is synthesized mainly from liver hepatocytes as a precursor polypeptide, which after oligomerization and cleavage, is split into two types of chains, called α and β (Kurosky et al. 1980). The α -chain contains a complement control protein (CCP) domain and the β -chain contains a serine proteinase (SP) related domain. In humans, but not in other primates, the Hp gene is found in two allelic variants, Hp1 and Hp2 (Maeda et al. 1984). The shorter α -chain (α_1) forms a link to one, and the longer chain (α_2) to two other α -chains. The two alleles, therefore, give rise to three different serotypes composed of two $\alpha_1\beta$ units (in Hp1-1), two $\alpha_1\beta$ and variable numbers of $\alpha_2\beta$ units (in Hp1-2), or variable numbers of $\alpha_2\beta$ units (in Hp2-2). The sizes of the three Hp proteins are Hp1-1 ~100 kDa; Hp2-1 ~ 120-220 kDa; and Hp2-2 ~ 160-500 kDa (Carter & Worwood, 2007).

Haptoglobin of cow (*Bos taurus*) contains an α -chain, the structure of which is similar to that of the human Hp2 α -chain. Interestingly, comparison of the structure of bovine Hp and human Hp2 suggests that the bovine gene arose by a duplication of the gene segment homologous to that duplicated in human Hp2 (Wicher & Fries, 2007). In ruminants, however, multiple electrophoretic bands of Hp have been observed, which are similar to those observed after electrophoresis of human Hp2-2 (Travis & Sanders, 1972); interestingly, no other Hp phenotypes seem to exist in these animals. In addition, it has been suggested that the structure of Hp in cattle, goat, sheep, and deer is similar to that of human Hp2 (Busby & Travis, 1978).

3.2 Functions

The main reported function of Hp is to bind hemoglobin (Hb). It is known that bacteria need iron (Fe) for their growth and they have developed sophisticated means to acquire Fe from Hb, like hemolysins. Hemoglobin has four Fe atoms and one hemolysed red blood cell might release ~ 250 million Hb molecules. In addition, by binding Hb, it inhibits its oxidative activity and its passage through the glomeruli (Lim et al. 1998). Hemoglobin also is highly toxic (Alayash, 2004) and its prosthetic group, heme, is lipophilic and intercalates

into cell membranes to disrupt the lipid bilayers. Iron present in heme catalyzes the generation of reactive oxygen species (ROS; Sadrzadeh et al., 1984). Moreover, Hp binds to apo A-1 to protect it from free radical-mediated damage and also to prevent HDL from forming adducts with other lipoprotein molecules (Salvatore et al., 2007). Another function of Hp is to inhibit both cyclooxygenase (COX) and lipoxygenase (LOX) activities, which provide a means to modulate responses to inflammation or infection that may be harmful to tissues (Saeed et al., 2007). Arredouani et al. (2005) showed evidence that Hp has the ability to selectively antagonize effects of LPS in vitro by suppressing monocyte production of TNF- α , IL-10, and IL-12. Haptoglobin is an established suppressor of T cell proliferation, exhibiting strong inhibition of Th2 cytokine release and weak inhibition of Th1 cytokine release (Arredouani et al., 2003).

3.3 Tissue distribution and factors that affect expression of haptoglobin

3.3.1 Tissue distribution

The expression of Hp is in abundant amounts in liver hepatocytes, which is the main source of Hp in blood (Yang et al., 1983). However, Hp has been detected in multiple tissues besides plasma such as in white and brown adipose tissue, placenta, lungs, arteries, testis, ovaries, and mammary gland tissues of dairy cows (Friedrichs et al., 1995; Kalmovarin et al., 1991; Yang et al., 1995; Hiss et al., 2004). The induction of Hp gene expression is mediated mainly by IL-6, which is the cytokine mediator for stimulation of Hp production in the liver hepatocytes of different species studied (Quaye, 2008).

3.3.2 Dietary factors

Two experiments were conducted by our team to investigate the effects of oral supplementation of the lactic acid-producing bacterium *Enterococcus faecium* EF212 alone or in combination with *Saccharomyces cerevisiae* (yeast) on mediators of the APR in feedlot steers (Emmanuel et al., 2007b). The effects of *E. faecium* alone or with yeast were evaluated. We found that feed supplementation with *E. faecium* had no effect on concentration of Hp in the plasma compared with control animals. However, feeding *E. faecium* and yeast increased plasma concentrations of Hp. Tourlomoussis et al. (2004) reported Hp concentration of 110 $\mu\text{g}/\text{mL}$ in the plasma of healthy beef cattle; however, cattle under different pathological conditions have average plasma Hp values of approximately 270 $\mu\text{g}/\text{mL}$. Results of *E. faecium* alone experiment, conducted by us, showed Hp concentrations of about 270 $\mu\text{g}/\text{mL}$ in control group and about 225 $\mu\text{g}/\text{mL}$ in experimental steers (Emmanuel et al., 2007b).

3.3.3 Mammary gland infections

Although it was believed that the liver is the main and the only source of Hp in cattle, in a recent study, Hiss et al. (2004) demonstrated that Hp also is expressed extrahepatically in mammary gland including parenchymal tissue, tissues surrounding the cisternal milk ducts, and in the teats. They also observed that milk Hp was increased 3 h after LPS challenge to one of the quarters, whereas elevation of blood Hp occurred 9 h after the challenge (Hiss et al., 2004). Concentrations of Hp in the blood and milk of cows before LPS challenge were at 32.8 and 0.9 mg/mL and increased 12 h after the LPS administration at 371.7 and 152.2 mg/mL , respectively (Hiss et al., 2004). In other studies conducted by Ohtsuka et al. (2001) and Pedersen et al. (2003) it was reported that concentrations of Hp in the milk increased in cows affected naturally from severe Gram-negative coliform mastitis and in those in which

mastitis was induced experimentally with Gram-positive *Streptococcus uberis*, respectively. Eckersall et al. (2001) also showed increased concentrations of Hp in the milk of cows with naturally occurring mild and moderate mastitis. These findings suggest that milk Hp might be a good biomarker of mastitis in dairy cows. In another study conducted by Åkersted et al. (2008) milk with detectable levels of Hp showed lower total protein and casein levels and higher somatic cell counts. It is not clear whether the relationship between Hp in the milk and differences observed in the milk composition is causal or simply the result of bacterial presence.

In a recent article Wenz et al. (2010) observed that concentration of Hp in the group of cows affected by Gram-negative bacterial mastitis was approximately twice that of the group infected by Gram-positive bacteria (1,126 vs 575 mg/mL, respectively). Moreover, cows in the mid-lactation group tended to have greater concentrations of Hp in the milk compared with those in the early lactation group (470 vs 891 mg/mL, respectively). Moreover, concentration of Hp was lower in cows with clinical mastitis during the Spring (345 mg/mL) vs those with clinical mastitis in the Summer (1,362 mg/mL), or Fall (1,105 mg/mL) and tended to be lower than those in the Winter (808 mg/mL).

3.3.4 Uterine infections

Different authors have reported an association among concentrations of Hp in the blood and diseases of the reproductive tract of dairy cows. For example, Smith et al. (1998) and Sheldon et al. (2001) showed an association between elevated concentrations of Hp in the postpartum period and metritis and Huzzey et al. (2009) indicated that cows with concentration of Hp of more than 1.0 g/L at 3 days in milk were 7 times more likely to develop metritis. Data from our team (unpublished) also support the fact that Hp is increased in dairy cows around calving especially in those affected by metritis. In a recent article Dubuc et al. (2010) indicated that blood Hp is a risk factor for reproductive disorders. They used a cut off concentration of Hp in blood, for cows with risk of metritis, at more than 0.8 g/L. They showed that Hp at more than 0.8 g/L, in the first 7 days of milk, is associated with more than 2 times the odds of developing metritis. In addition, the same authors found that elevated concentration of Hp is a risk factor for purulent vaginal discharges and cytological endometritis at 35 d in milk.

3.3.5 Lameness

Different investigators have reported increased concentrations of Hp in the serum of cows with claw disorders. Interestingly, most of them have suggested that all claw disorders, whether infectious or non-infectious, lead to a systemic APR (Shearer et al., 1996; Bergsten et al., 1998; Hoblet & Weiss, 2001). For example, Smith et al. (2010) showed that concentrations of Hp in the serum of healthy cows, free of lameness, were below the detection limit of <1.0 mg/dL. Lamé cows, with infectious or non-infectious claw disorders, were found to have either increased serum Hp of more than 1.0 mg/dL, or found with concentrations lower than 1.0 mg/dL. Cows that tested positive for Hp had concentrations ranging between 37 and more than 100 mg/dL. Additionally, Jawor et al. (2008) demonstrated that increased concentrations of Hp in the serum are associated with lameness in cattle; however, the authors caution that there are also lame cows with undetectable Hp levels in the serum.

3.3.6 Fatty liver and downer cow syndrome

In a study conducted by us we showed that in cows fed high amounts of grain, to induce fatty liver in periparturient cows, concentrations of plasma Hp were similar to those of control cows before parturition, but after parturition plasma Hp increased markedly (ca. 200 mg/dL) and remained higher than that of control cows on days 3, 8, and 12 postpartum (Ametaj et al., 2005a). By day 14 postpartum, plasma Hp decreased to prepartal concentrations (ca. 40 mg/dL) in fatty-liver cows and remained at that level up to 36 d postpartum.

3.3.7 Age-related factors

Alsemgeest et al. (1995) showed that healthy newborn calves had no detectable amounts of Hp in the serum. On the other hand, only 25% of the newborn calves suffering from different diseases immediately after birth had detectable concentrations of Hp. It is possible that the assay for measuring Hp in the serum has affected detection of Hp during the 1990s. In 1999 Katoh & Nakagawa showed association of Hp with the high-density (HDL) and very-high density (VHDL) lipoprotein fractions but not with those of chylomicrons, VLDL, and LDL fractions in the sera of calves experimentally infected with *Pasteurella hemolytica*. Concentration of Hp in the sera of calves with pneumonia were <0.01, 194, 717, 940, 722, and 524 mg/mL on d 0, 1, 2, 3, 4, and 7 of infection with *P. hemolytica*, respectively. Orro et al. (2008) showed that Hp in the plasma of the newborn calves between 0-21 d were between 100-350 mg/mL.

4. Lipopolysaccharide-binding protein

4.1 Structure and tissue distribution

Bovine LBP is a 50-kDa polypeptide that consists of 481 amino acids (Khemlani et al., 1994). The protein is mainly synthesized by hepatocytes and is released into the bloodstream as a 60 kDa glycoprotein (Schumann et al., 1990; Khemlani et al., 1994). Its amino acid sequence reveals an 86% similarity compared to human LBP (Khemlani et al., 1994). Moreover, a recent investigation, showed that mRNA LBP is widely expressed extrahepatically, in the gastro-intestinal tract (i.e., submandibular salivary gland, rumen, reticulum, omasum and abomasum), lung, female reproductive system (i.e., ovary and uterus), thyroid gland, nervous system (i.e., brain and cerebellum), and mammary gland (i.e., parenchyma, cistern, and teat) of cattle. Moreover, research reveals that the highest expression of bovine LBP gene is observed in the reticulum (72-fold) and parotid gland (50-fold) compared with 1-fold in the liver (Rahman et al., 2010). These results show that epithelial mucosal tissues of the ruminant particularly forestomach secrete LBP and that LBP might play a significant role in mucosal immunity. It is worth mentioning that besides LBP there is another similar protein known as bactericidal permeability increasing protein (BPI) and that both LBP and BPI belong to the family of lipid transfer/LPS binding proteins (Bingle & Craven, 2004). In cattle, both genes are closely located on the chromosome 13. Interestingly, both LBP and BPI interact with bacterial endotoxin, however, the mechanism by which they deal with LPS is different. Lipopolysaccharide-binding protein causes disaggregation of LPS as part of its role in promoting LPS signaling, whereas BPI inserts itself into LPS aggregates, promotes formation of larger aggregates, and interferes with the ability of LBP to disperse large LPS aggregates (Tobias et al., 1997). Lipopolysaccharide-binding protein is considered to be

proinflammatory, as it induces the LPS signaling, whereas BPI as anti-inflammatory because it removes the LPS molecules without inducing the LPS signaling (Elsbach & Weiss, 1998, Fenton & Golenbock, 1998).

4.2 Functions

The main known function of LBP is to bind and transport LPS either to immune cells or lipoprotein particles (Gallay et al., 1994). The principle mechanism by which this occurs is through the ability of LBP to dissociate LPS aggregates into LPS monomers. In this process other proteins like CD14 help LBP to transfer LPS. In fact, CD14 is found in two isoforms, as a membrane-bound (mCD14) and a free soluble molecule (sCD14). Interestingly, when blood LPS is at low concentration LBP directs it to the macrophages and when LPS is at greater concentration it directs it to lipoprotein particles, especially HDL (Gallay et al., 1994). The LBP-LPS complex interacts either with mCD14, which is expressed by monocytes, macrophages, and neutrophils (Schumann et al., 1994) or with sCD14 that transfers LPS to HDL particles (Tobias et al., 1999). Binding of LPS to immune cells triggers the release of cytokines, which are responsible for stimulating the APR (Moshage, 1997). Toll-like receptor (TLR)-4 and MD-2 are also involved in the activation of both monocytic cells and those that do not express CD14 during binding of LPS (Chow et al., 1999). It is also known that CD14 facilitates the binding and activation of TLR4/MD-2 complex (Fitzgerald et al., 2004). Interestingly, sCD14 is also present in bovine milk. For example, milk concentration of sCD14 was shown to be increased following the LPS challenge or *Escherichia coli* infection in dairy cows (Lee et al., 2003a, b).

4.3 Factors that affect expression of LBP

4.3.1 Dietary factors

A study by our team indicated that the amount of grain in the diet affects concentration of LBP in the plasma of dairy cows (Emmanuel et al. 2008). Thus, cows fed diets containing high proportions of barley grain (45%) had greater LBP concentration (10 µg/mL) compared with control cows (5.7 µg/mL) that were fed no barley grain. The same study reported that concentration of LBP in the plasma differed between cows fed diets containing 15% (4.6 µg/mL) and 30% (6.5 µg/mL) barley grain. Furthermore, no differences were found in plasma LBP levels between groups of cows fed 0 and 15% barley grain (i.e. 6 µg/mL). In an investigation by Khafipour et al. (2009) they showed similar results with elevated blood and milk LBP (18.2 vs 53.1 µg/mL and 3.02 vs 6.94 µg/mL) during induced subacute ruminal acidosis (SARA). The reason for increased LBP in the blood circulation of cows fed high-grain diets has been related to translocation of endotoxin into the systemic circulation (Emmanuel et al., 2008; Khafipour et al., 2009). Research conducted in beef steers (i.e., backgrounding and feedlot cattle) has also shown that feeding high amounts of grain (i.e., barley grain) induces an inflammatory state in those animals (Ametaj et al., 2009). The same authors report that concentration of LBP in steers fed a finishing diet shows peak values of LBP within 3 wk from the initiation of the diet (23 µg/mL).

In an effort to find a solution against grain-induced inflammatory states in dairy cows we fed cows barley grain steeped in lactic acid for 48 h and found that treatment was associated with lowered concentration of LBP in the plasma (Iqbal et al. 2010). Different investigators have studied the potential application of direct-fed microbials as prophylactic tools against ruminal acidosis. In a study conducted by our team we infused *Enterococcus faecium* EF212 (*E. faecium*; 6×10^{10} cfu/d) alone or in combination with *Saccharomyces cerevisiae* (*S. cerevisiae*; 6×10^{10} cfu/d) in the diet of feedlot steers fed 87% steamed rolled barley grain and 8%

whole-crop barley silage for a period of 3 wk (Emmanuel et al., 2007b). Data showed that feeding *E. faecium* and yeast increased plasma concentrations of LBP versus controls on both day 17 and 21 of the experimental period (22 vs 10 $\mu\text{g}/\text{mL}$ and 40 vs 25 $\mu\text{g}/\text{mL}$, respectively).

It is known that during early lactation the concentration of glutamine, the most abundant amino acid in the plasma and milk, is lowered in dairy cows (Meijer et al., 1993). Therefore, we conducted a blood infusion study administering daily 0 (control), 106, and 212 g/d of L-glutamin to periparturient dairy cows for 7 consecutive days starting on d 1 after calving. Data showed increased LBP concentrations by administration of L-glutamin (10.8 vs 35.6 and 50.0 $\mu\text{g}/\text{mL}$, respectively; Jafari et al., 2006).

In another investigation involving oral supplementation of feedlot cattle, fed with 86% barley grain and 9% barley silage, with four different amounts of cinnamaldehyde (0, 400, 800, and 1,600 mg/steer) we showed lowered blood concentration of LBP in relation with the amount of cinnamaldehyde in the diet (1.63, 2.36, 1.78, and 0.98 $\mu\text{g}/\text{mL}$; Yang et al., 2010).

4.3.2 Mammary gland infections

Concentrations of LBP in the serum and milk of cows with natural or induced clinical mastitis was reported to be greater than in dairy cows with healthy udders (Zeng et al., 2009). Interestingly, blood LBP increased earlier and remained longer at high levels compared with other APP such as SAA following an intramammary challenge with *Escherichia coli*, *Mycoplasma bovis*, or *Pseudomonas aeruginosa* (Bannerman et al., 2005, Kauf et al., 2007). Other investigators also have shown that intramammary challenge with LPS or *E. coli* increases both blood and milk LBP (Bannerman et al., 2004; Kauf et al., 2007). For example in a recent experiment, mastitis was induced with a dose of 1,500 cfu of *E. coli* in one quarter of six cows and inoculation was repeated in another quarter after an interval of 14 days (Suojala et al., 2008). Concentrations of LBP in both milk and blood were found to be greater in this experiment compared with those of Bannerman et al. (2004). Thus, Suojala et al. (2008) reported that the basic concentrations of serum LBP before the LPS and *E. coli* challenge were at 10.8 $\mu\text{g}/\text{mL}$ after the first challenge and 10.0 $\mu\text{g}/\text{mL}$ after the second one. Serum LBP started to increase rapidly in both groups of cows and peaked at 36 h after challenge, being on average 148.6 $\mu\text{g}/\text{mL}$ after the first challenge and 108.9 $\mu\text{g}/\text{mL}$ after the second one. Interestingly, milk LBP was associated with somatic cell counts (SCC) regardless of the infection status. Milk samples containing > 250,000 and those containing < 250,000 had blood LBP levels at 12.78 and 0.33 $\mu\text{g}/\text{mL}$, respectively.

4.3.3 Fatty liver and downer cow syndrome

As mentioned before, production of LBP is stimulated by LPS, which might affect different metabolic pathways in dairy cattle. Therefore, different metabolic disturbances might be triggered either directly by endotoxin or indirectly by the inflammatory response (i.e., cytokines) initiated by endotoxin. Previous studies have supported the hypothesis that impaired insulin sensitivity mediated by cytokines such as TNF- α activates lipolysis and decreases glucose production in cows with fatty liver (Ametaj et al., 2005a, Bradford et al., 2009).

Recent data have suggested that blood LBP might be used as a biomarker for downer cow syndrome (DCS). An observational study by Ametaj et al. (2010) showed a strong

association between DCS and plasma LBP (a 10-fold increase) at 7 d before parturition. Moreover, results indicated that cows affected by DCS had lower anti-LPS IgG and greater concentrations of anti-LPS IgM. Involvement of LBP in different metabolic disturbances suggests it can be used as a valuable diagnostic biomarker in dairy cattle.

4.3.4 Age-related factors

Hoadagoda et al. (1995) and Schrödl et al. (2001) showed presence of LBP in several weeks old calves. They reported values of serum LBP ranging between 1.6 - 2.3 µg/mL. Both groups of investigators infected calves with *Mannheimia haemolytica* (*Pasteurella*) and observed a sharp increase (4- to 7-fold) in the serum LBP several hours (6 h) after the challenge. On the other hand they (Schrödl et al. 2001) reported that Hp was increased only 12 h after the inoculation with bacteria. Based on those results they suggested to use LBP as a biomarker of disease in calves infected by *M. haemolytica*. Furthermore, in a study conducted by Nikunen et al. (2007) calves with clinical respiratory disease (i.e., *Pasteurella multocida*) had elevated concentrations of LBP in the serum compared to noninfected healthy calves (13.5 vs 6.3 µg/mL).

5. C-reactive protein

5.1 Structure

C-reactive protein belongs to the pentraxin family of calcium-dependent ligand-binding-proteins consisting of 5 identical 23-kDa protomers arranged symmetrically around a central pore. Each protomer consists of 206 amino acids folded into 2 antiparallel β sheets. In the assembled protein, all protomers have the same orientation. Thus, each protomer has a recognition face with a phosphocholine (PCh) binding site consisting of two coordinated Ca ions adjacent to a hydrophobic pocket, and an effector face, where complement C1q binds and Fcγ receptors are presumed to bind (Shrive et al., 1996; Thompson et al., 1999). Binding of PCh to CRP is mediated by 2 key amino acid residues: Phe-66 that provides hydrophobic linkages with methyl groups of PCh, and Glu-81 that interacts with positively charged choline nitrogen (Agrawal et al., 2002; Black et al., 2003). Asp-112 and Tyr-175 are the critical residues required for CRP binding to complement C1q (Agrawal & Volanakis, 1994; Agrawal et al., 2001).

5.2 Functions

C-reactive protein is a highly conserved plasma protein that participates in systemic responses to inflammation. It binds specifically to host molecules exposed during apoptosis or found on surfaces of pathogens. More specifically, CRP has a Ca-dependent binding specificity to PCh. The CPR synthesis increases within hours of infection or tissue injury and has thus been considered part of the APR (Black et al., 2004; Volanakis, 2001). Its ability to recognize pathogens and to mediate their elimination by recruiting the complement system proteins and phagocytic cells makes CRP an important constituent of the first line of innate host defense. Furthermore, the protein appears to play a key role in the clearance of apoptotic and necrotic host cells, thus contributing to restoration of normal structure and function of injured tissues (Volanakis, 2001). The discovery of CRP stemmed from studies of patients with *Streptococcus pneumoniae* infection where a protein was found that could precipitate the C polysaccharide of the bacterial cell wall during acute phase of the illness

(Tillet & Francis, 1930). Phosphocholine was later identified as the specific ligand for CRP in the pneumococcal C polysaccharide, part of the teichoic acid of the pneumococcal cell wall (Volanakis & Kaplan, 1971).

The main biological function of CRP is particle recognition on pathogens and damaged cells of the host followed by mediation of their removal through activation of the complement cascade and phagocytosis. As mentioned previously, the main ligand of CRP is PCh, which is found on a number of bacterial species. Membrane phospholipids of eukaryotes also contain PCh but their head groups are only accessible to CRP in damaged or apoptotic state (Kaplan & Volanakis, 1974; Volanakis & Wirtz, 1979). The other well-recognized ligands of CRP are phosphoethanolamine, chromatin, histones, fibronectin, small nuclear ribonucleoproteins, laminin, and polycations (Black et al., 2004). Binding of CRP to these nuclear constituents is Ca dependent and has been observed in nuclei of necrotic cells at sites of inflammation (Gitlin et al., 1977). In addition to interacting with various ligands, CRP can activate the classical complement pathway, stimulate phagocytosis, and bind to immunoglobulin IgG receptors (FcγR). C-reactive protein bound to a multivalent ligand is recognized by C1q and can efficiently initiate the formation of a C3 convertase through the classical complement pathway (Volanakis, 2001). This cascade efficiently results in recruitment of the opsonic function of the complement system, but not its pro-inflammatory and membrane damaging effects, which requires cleavage of C5 (Volanakis, 2001). The opsonic properties of CRP have been demonstrated for both macrophages and neutrophils (Volanakis, 2001). Indeed, phagocytosis of CRP-opsonized particles by mouse monocytes and neutrophils was shown to proceed through the FcγRI (Mold et al., 2001). Enhancement of phagocytosis by CRP is also mediated indirectly by opsonic complement fragments attached to CRP ligands as a result of CRP-initiated complement activation (Edwards et al., 1982).

5.3 Factors affecting its concentration

Plasma CRP is produced mainly by hepatocytes, predominantly under transcriptional control by IL-6, although other sites of local CRP synthesis and possibly secretion have been suggested. De novo hepatic synthesis starts very rapidly after a single stimulus. The plasma half-life of CRP is about 19 h and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate (Vigushin et al., 1993), which thus directly reflects the intensity of the pathological process(es) stimulating production of CRP. When the stimulus for increased production completely ceases, concentrations of circulating CRP fall rapidly, at almost the rate of plasma CRP clearance. Concentrations of CRP in the serum of healthy dairy cows range between 10-30 µg/mL (Lee et al., 2003c; Morimatsu et al., 1989, 1991). However, these levels can dramatically rise following natural or experimental infections. The following factors have been reported to affect CPR levels in dairy cows.

5.3.1 Lactation

The circulating CRP was observed to increase a few days after parturition in dairy cows but it was attributed to tissue injury in the uterine epithelium (Morumatsu et al., 1991). Interestingly, serum CRP also increased gradually as milk production increased during peak lactation in dairy cows. Thus, the lactation-induced pattern of CRP might be useful in monitoring milk production and progression of mastitis in dairy cows (Morimatsu et al., 1991). In a recent article we indicated a strong relationship between rumen endotoxin and plasma CRP and suggested a potential role of CRP in milk fat depression syndrome in dairy

cows (Emmanuel et al., 2008). We proposed that CRP might prevent interaction of apo-C-II with lipoprotein lipase to shift lipoprotein particles toward liver and as a result lowering transferring of lipid loads into the mammary gland (Zebeli & Ametaj, 2009).

5.3.2 Body condition score (BCS), age, and pregnancy status

An inverse relationship was found in serum CRP levels and BCS of dairy cows and subsequent regression analysis indicated that a unit increase in BCS decreased CRP level by 20.2 $\mu\text{g}/\text{mL}$ (Lee et al., 2003c). On the other hand, age of the cow correlated poorly with serum CRP levels. Interestingly, concentrations of CRP in the serum increased during the first 4 mo of gestation (34.5 $\mu\text{g}/\text{mL}$) and gradually decreased to nadir levels (4.9 $\mu\text{g}/\text{mL}$) during late gestation (Lee et al., 2003c, Turk et al., 2008). Although it is not clear what is the function of CRP during gestation in cattle, human research indicates that high concentrations of CRP during pregnancy have been associated to complications during its course (Teran et al., 2001). Elevated CRP levels at first trimester may represent a risk to gestational preeclampsia (Wolf et al., 2001). On the other hand, Sacks et al. (2004) observed a very early increase of circulatory CRP at 4 wk of gestation in non-obese young pregnant women, suggesting a maternal low-grade inflammatory response during the earliest phases of ovule implantation.

5.3.3 Stress and disease

Concentration of CRP in the serum of cows is invariably affected by stress. Handling and/or sampling stress has been shown to influence serum CRP in dairy cows; however, the effect subsides within 48 h (Lee et al., 2003c). Diseases accompanied by inflammatory reactions induce greater stress and in turn elevate CRP levels in dairy cows. Lee et al. (2003c) categorized disease in dairy cows into inflammatory (for example, acute and chronic mastitis, foot rot, endometritis, and pneumonia) and non-inflammatory (for example, abortion, reproductive disorders, stillbirth, and ovarian cysts) groups. The authors reported greater concentrations of CRP in both groups of diseased cows whether classified as inflammatory or non-inflammatory, and indicated that CRP levels might be useful in monitoring herd health and disease surveillance in dairy cows. The amount of CRP (i.e., in optical density values) in the diseased cows was 3-3.5 fold greater than the healthy cows (Lee et al., 2003c).

5.3.4 Mastitis

Mastitis is an important production disease of dairy cattle commonly caused by infectious agents in the environment. The results regarding utilization of milk CRP as an indicator of mastitis have been controversial. Thus, Schrödl et al. (1995) reported as much as 10-fold increase in the concentration of CRP in the milk of cows with mastitis (1,083 ng/mL) compared to normal healthy cows (82 ng/mL). On the other hand, Hamann et al. (1997) showed that the capacity of the milk CRP to distinguish between healthy and mastitic quarters was poor, and the correlation between the concentration of the CRP in the milk and SCC was low ($r = 0.32$).

5.3.5 Age-related factors

Only a few studies have addressed blood CRP in young ruminants. Schrödl et al. (2003) showed presence of CRP in all plasma samples of calves before the first colostrum intake,

and a greater concentration in the blood 1 d after colostrum application. The authors postulated that the increase of the CRP concentration (1 d postpartum) is affected by the passive transfer of CRP from colostrum to blood. The same authors showed that feeding lactulose, a prebiotic compound, further increased the levels of CRP in the plasma of calves fed colostrum.

In conclusion, CRP, like other APP, is an important constituent of the first line of innate host defense. Most evidence for these functions to date has been obtained in studies using human and murine CRP. Even though increased concentrations of bovine CRP during naturally occurring infections and a correlation with herd health status have been reported, CRP has not been fully considered as an APP in cattle.

6. Soluble cluster of differentiation 14

6.1 Structure

Soluble CD14 is a single chain protein with a molecular weight of about 50-53 kDa and spans approximately 348 amino acids in length. Structure analysis by proteolytic cleavage has shown that the molecule is made of two tightly folded domains, the main binding site for LPS (Juan et al., 1995; McGinley et al., 1995).

6.2 Functions

The bovine cluster of CD14 is an important player in host innate immunity in that it mediates host defense against Gram-negative bacterial infections and also confers immunity against viral infections (Chen et al., 1999; Haziot et al., 1996). Two forms of CD14 have been reported; a membrane bound form (mCD14) and a soluble (sCD14) form (Ulevitch & Tobias, 1995). The sCD14 helps to carry LPS in cells that lack mCD14 (e.g., endothelial and epithelial cells). The mCD14 is attached to the surface of myeloid cells (monocyte/macrophages) via glycosyl-phosphatidyinositol tail (Haziot et al., 1998). Moreover, CD14 is required for the recognition of other bacterial products including peptidoglycan, lipoteichoic acid (LTA), and lipoarabinomannan (Gupta et al., 1996; Pugin et al., 1994; Savedra et al., 1996). The CD14 gene in cattle was initially cloned and sequenced by Ikeda et al. (1997) and recently by the bovine genome project. In this review we will focus on sCD14 as an APP.

The serum sCD14 is believed to originate from enzymatic cleavage of its membrane homologue mCD14 through the action of specific phospholipases or proteases (Bazil et al., 1989, Sohn et al., 2007). It was first described by Maliszewski et al. (1985) as a culture-supernatant blocking factor, soluble My 23, an antigen from human myeloid cells that was able to block staining of monocytes by anti-CD14 monoclonal antibodies. Together with LBP, sCD14 plays a crucial role in enabling cellular responses to Gram-negative bacterial LPS by shuttling LPS between LPS micelles to HDL (Kitchens & Thompson, 2005; Wurfel et al., 1995).

Soluble CD14 facilitates transfer of LPS to lipoproteins, preventing over stimulation during the inflammatory responses (Maliszewski, 1991; Schutt et al., 1992). Transfer of LPS to HDL occurs either by the direct action of LBP or by a two-step reaction in which LPS is first transferred to sCD14 and subsequently to HDL. However, the two-step pathway of LPS transfer to HDL is strongly favored over direct transfer (Wurfel et al., 1995). Interestingly, movement of LPS from LPS-sCD14 complexes to HDL neutralizes the capacity of LPS to stimulate neutrophils.

Soluble CD14 also functions as a soluble receptor for bacterial LPS to cells that do not express CD14 such as epithelial and endothelial cells and thereby activates TLR-4 and the release of cytokines (Frey et al., 1992; Kitchens & Thompson, 2005). Toll-like receptor 4 mediates cellular responses to microbial LPS and acts as a co-receptor with mCD14 for LPS (Sohn et al., 2007).

Soluble CD14 also has pro-inflammatory activities in the extravascular compartments where it increases resistance to bacteria. In breast milk, for example, sCD14 has been associated with reduced occurrence of gastrointestinal infections in infants (Labéta et al., 2000). Moreover, sCD14 isolated from mouse, human, and bovine subjects have been involved in activation of B cell activity (Filipp et al., 2001). Therefore, it has been hypothesized that consumption of cow milk containing sCD14 might confer similar beneficial effects (Lee et al., 2003a). In a bovine model of intramammary *Escherichia coli* infection, co-injection of recombinant bovine sCD14 with the bacteria accelerates the recruitment of neutrophils and clearance of bacteria (Lee et al., 2003b).

6.3 Tissue distribution and factors affecting sCD14 expression

Expression of sCD14 in human subjects has been detected in the lung, heart, thymus, and liver; however, expression in the liver is much greater than the other tissues. Therefore, liver is considered to be the major source of sCD14 in circulation. To our best knowledge, no information about sCD14 expression in cattle liver has been reported so far.

Another important source of sCD14 are immune cells. Thus, human monocytes express high levels of CD14 ($\sim 10^5$ receptor/cell) whereas mCD14 expression on neutrophils is much lower ($\sim 3 \times 10^3$ receptors/cell). Expression of mCD14 on tissue macrophages can vary depending upon their origin. In cattle CD14 is expressed at 99,500-134,600 receptors, on the cell membrane of monocytes and to a lesser extent, at 1,900-4,400 receptors on neutrophils (Antal-Szalmás et al., 1997; Paape et al., 1996). An intracellular pool of CD14 exists in bovine PMN and is capable of translocating to the cell surface as mCD14 (Paape et al., 1996). Research conducted by Sohn et al. (2007) indicated that mCD14 expressed on bovine neutrophils is a source of plasma sCD14 in cattle. Moreover, they showed that sCD14 is shed from bovine neutrophils after stimulation by LPS.

A third major source of sCD14 is the mammary gland, which in cows is at concentrations around 1-6 $\mu\text{g}/\text{mL}$ (Bannerman et al., 2003; Bannerman et al., 2004; Lee et al., 2003a,b). Interestingly, the cellular source of sCD14 in human milk was shown to be mammary epithelial cells, which secrete in culture a slightly smaller form of sCD14 than that released by monocytes (Labéta et al., 2000). Apparently, there is no research in dairy cows to indicate the source of CD14 in the mammary gland. Interestingly, Sohn et al. (2004) reported that in bovine milk the molecular mass of sCD14 ranges between 53 and 58 kDa, very similarly with the forms found in the blood plasma.

Various infectious diseases have been shown to increase sCD14 in the serum (Kitchens et al., 2001). For example, circulatory sCD14 increased in respiratory tract secretions of patients suffering from acute respiratory distress syndrome, and in cerebrospinal fluid of patients with bacterial meningitis.

Concentration of sCD14 in the milk, from healthy quarters of dairy cows, was reported to be at 6.90 $\mu\text{g}/\text{mL}$ (Lee et al. 2003a,b). Intra-mammary inflammation, induced by LPS challenge, increases milk SCC in dairy cows, which in turn increases concentrations of sCD14 in the milk from the infected quarters. In addition, stage of lactation also affects concentration of sCD14 in bovine milk with higher levels observed during 0-4 d postpartum than other

periods of lactation (Bannerman et al., 2004; Lee et al., 2003a). However, in normal human breast milk much greater concentrations of sCD14 (14.84 $\mu\text{g}/\text{mL}$) have been reported (Labéta et al., 2000).

6.4 Utilization of sCD14 for treatment of bacterial mastitis

Intramammary injection of recombinant bovine sCD14 together with low concentrations of LPS in lactating dairy cows induced recruitment of neutrophils when compared to either LPS or CD14 alone (Wang et al., 1997). Moreover, administration of a high concentration of LPS in the mammary gland causes an increase of sCD14 in the milk, attributed to shedding of mCD14 from recruited neutrophils, and might play a role in modulating the inflammatory responses during coliform mastitis in cows (Paape et al., 2002). Furthermore, recombinant bovine sCD14 was able to lower the severity of intramammary gland infection by *E. coli* in a mouse model of mastitis (Leet et al., 2003a) and also decrease the severity of infection in dairy cows after intramammary challenge with *E. coli* (Leet et al., 2003b).

7. Ceruloplasmin

7.1 Structure

Ceruloplasmin (Cp; or ferroxidase) is a protein of the α -2 globulin fraction of the bovine serum. This protein belongs to the family of multicopper oxidases. Serum Cp is synthesized mainly in the liver hepatocytes (Løvstad, 2006). However, the protein is expressed in other tissues as indicated in the next section of this review. Dooley et al. (1981) were the first to characterize bovine Cp. It is the product of an intragenic triplication and is comprised of three homologous domains (Yang et al., 1986). In humans, Cp is a single polypeptide chain of 1,046 amino acids (Endo et al., 1982), whereas bovine Cp is comprised of 1,063 amino acids (Zimin et al., 2009). Early studies estimated bovine Cp at a MW of 100 kDa (Dooley et al., 1981), whereas more recent comparative studies between bovine and human Cp indicated MWs of 125.1 and 129.8 kDa, respectively (Boivin et al., 2001). Bovine Cp includes six copper atoms as an integral part of the native protein (Zgirski & Frieden, 1990). Liver hepatocytes produce apo-Cp that has no copper (Cu) in it (Macintyre et al. 2004). Subsequently, 7 Cu atoms are added to the protein (Mukhopadhyay et al. 1997), which establishes a more stable product, holo-Cp (Terada et al. 1995). Almost 90% of Cp in blood is in the form of holo-CP (Matsuda et al., 1974).

7.2 Functions

Ceruloplasmin contains more than 95% of plasma Cu and might play a role in Cu homeostasis (Martinez-Subiela et al., 2007). However, its role in Fe homeostasis has overshadowed its Cu-related function. Therefore, the main reported function of Cp is ferroxidation or facilitation of oxidation of Fe^{2+} to Fe^{3+} and its subsequent binding to apo-ferritin (Fleming et al., 1991). The ferroxidase activity of Cp is required for proper Fe homeostasis and lack of Cp leads to internalization and degradation of ferroportin, an Fe exporter (De Domenico et al., 2007). Furthermore, genetic defects of the Cp gene cause aceruloplasminemia, a rare disease with clinical manifestations, including retinal degeneration, diabetes mellitus, and neurological symptoms, which include ataxia, involuntary movements, and dementia (Miyajima, 2003). Humans with aceruloplasminemia also show Fe accumulation in various organs including the retina, liver, and brain, but there is no evidence of Cu deficiency or abnormalities in Cu metabolism (Jeong & David, 2003). It

has also been reported that Cp may play a role in scavenging reactive oxygen species (Healy & Tipton, 2007).

7.3 Tissue distribution and factors that affect its expression

7.3.1 Tissue distribution

Serum concentration of Cp increases during inflammation, infection, and trauma largely as the result of increased gene transcription in hepatocytes, mediated by the inflammatory cytokines (Gitlin, 1988). Although the liver is the predominant source of serum Cp, extrahepatic expression of Cp gene has been demonstrated in many other tissues including spleen, lung, testis, brain, uterus, yolk sac, and placenta (Aldred et al., 1987, Thomas & Schreiber, 1989; Thomas et al., 1989). Ceruloplasmin also was detected in the milk and mammary gland of dairy cows (Tabrizi et al., 2008).

7.3.2 Stage of lactation and breed

The half-life of serum Cp is around 5.5 days, and studies demonstrate little or no exchange of Cu bound to Cp following its synthesis (Gitlin & Janeway, 1960; Sternlieb et al., 1961). Interestingly, failure to incorporate Cu during synthesis results in the secretion of an unstable apo-Cp moiety devoid of ferroxidase activity (Holtzman et al., 1970). In the normal adult human about 10% of the total circulating Cp is found as the apoprotein, which is rapidly catabolized with a half-life of about 5 h (Matsuda, 1974). Consistent with these data, an increase in the hepatic Cu pool results in a sustained increase in the concentration of Cp in the serum, whereas a decrease, as occurs in nutritional Cu deficiency, results in a marked decrease in serum Cp (Holtzman et al., 1966; Olivares & Uauy, 1996). Under normal circumstances the hepatic Cu pool is not rate-limiting for holo-Cp synthesis, as concentration of Cp in the serum concentration increases rapidly during infection, trauma, and pregnancy while the ratio of apo- to holo-Cp is maintained (Matsuda et al., 1974).

The basal oxidase activity of Cp in the plasma of female Angus calves, Holstein dairy cows, and steers (Angus and Angus x Simmental) was estimated at 1.31, 60, and 21.9 $\mu\text{g}/\text{mL}$, respectively (Cerone et al., 2000, Hansen et al., 2008, Nazifi et al., 2009); whereas the basal concentration of Cu was approximately 0.75 and 1.14 $\mu\text{g}/\text{mL}$ in calves and steers, respectively (Cerone et al., 2000, Hansen et al., 2008).

A recent study of Hussein et al. (2011) reported concentrations of Cp in the serum of dairy cows during different stages of lactation (3–1 wk prepartum; 0–1 wk; 3–5 wk, and 15–18 wk postpartum) and showed greater concentration during 0–1 wk postpartum. Interestingly, these authors found that the activity of Cp is lower in the serum and in EDTA-treated plasma compared to heparinized plasma. They recommended heparinized plasma as the best way to preserve blood for measurement of Cp in dairy cow (Hussein et al., 2011).

A study involving supplementation of Cu in steers showed that concentration of Cp in plasma was increased in association with liver Cu. They found that 10 mg of Cu/kg of DM increased plasma and liver Cu, and concentration of Cp compared with steers supplemented with 5 mg of Cu/kg of DM. In addition, the same study demonstrated that feeding steers copper glycinate was associated with greater plasma Cp than with copper sulfate (19.0 vs. 14.6 $\mu\text{g}/\text{mL}$) (Hansen et al., 2008).

7.3.3 Ceruloplasmin during disease states

Ceruloplasmin has been evaluated as a marker of animal health and welfare (Skinner, 2001). Several studies in cattle indicate its diagnostic use (Sheldon et al., 2002, Szczubiał et al.,

2008). During administration of LPS (2.5 mg/kg body weight) in steers there is a decrease in concentration of Cp in the serum 2–3 h after LPS infusion (Carroll et al., 2009). The latter authors suggested that the decline in serum Cp might be related to Fe redistribution in the host blood, to lower Fe circulation in blood in order to prevent bacteria from that essential nutrient (Weinberg, 1984).

In another study involving infection of the mammary gland, with *Staphylococcus aureus* in dairy cows, it was demonstrated an increased concentration of Cp in the mammary gland in infected quarters compared to the healthy ones. Studies in young animals have shown that concentration of Cp in the serum increases during induced pneumonic pasteurellosis, with the highest concentration observed 2 and 4 h after the inoculation (Fagliari et al., 2003).

In a recent investigation Chassagne et al. (1998) suggested a breakpoint level of Cp over 143 µg/mL (oxydase units) in dairy cows as a reliable threshold to detect early mastitis cases. They showed that 83.5% of the cows that had lower than 49 Cp oxidase units in the serum were unaffected by mastitis versus 16.5% that were affected. Interestingly the same authors showed that high precalving plasma ceruloplasmin oxidase activity was a risk factor for early clinical mastitis.

In sheep and cattle, serum Cp has been used to a limited extent to investigate Cu deficiency (Lorentz & Gibb, 1975, Mills et al., 1976). This was based on the fact that Cu deficient animals injected with Cu show an increased Cp activity and blood Cu concentrations thereafter (Bingley & Anderson, 1972, Lorentz & Gibb, 1975). Another study by Cerone et al. (2000) demonstrated that in Cu deficient (Cu < 0.35 µg/mL) calves, plasma activity of Cp was lower (i.e. 0.62 µg/mL) compared to control calves (i.e. Cu < 0.75 µg/mL; Cp = 1.31 µg/mL).

The low level of plasma Cp might lead to decrease antimicrobial activity of phagocytes (Boyne & Arthur, 1981). It is anticipated that the Cp might deliver Cu to enzymes such as lysyl oxidase; ceruloplasmin might transport Cu to maintain the activity of leukocyte enzymes involved in the respiratory burst (Cerone et al., 2000).

A recent study demonstrated variations in Cp levels during intramammary administration of antibiotics alone (cefotaxime = 250 mg; 6 doses in total) or in combination with proteolytic enzymes (wobenzym drg and 100 mg of cefotaxime; 5 doses in total) in cows with clinical mastitis (Bakeš & Illek, 2006). In fact, concentration of Cp in the plasma before therapy was 25.77 µg/mL in both control and treated animals; however, concentration of Cp increased to 37.22 and 31.49 µg/mL after the treatment with antibiotics alone or in combination with proteolytic enzymes, respectively. Interestingly, the study of Bakeš & Illek (2006) showed that the enzyme therapy lowers the need for the use of antibiotics in dairy cows.

Another study involving bovine *Tropical Theileriosis* demonstrated alterations in the blood APP, including Cp in serum. The cut-off point for concentration of Cp in the plasma of Holstein dairy cows to be recognized as affected by the disease was suggested to be greater than 64 µg/mL, with 80% sensitivity for detection (Nazifi et al., 2009).

In conclusion, the potential to use serum Cp as a biomarker of disease state in dairy cattle is not very well established yet. Although, it was reported by several investigations that concentrations of Cp increase during administration of endotoxin (Conner et al., 1989), clinical mastitis (Tabrizi et al., 2008), or *Tropical Theileriosis* (Nazifi et al., 2009) further research is warranted to evaluate the functions and benefits of measuring Cp in cattle health.

8. Lactoferrin

8.1 Structure

Lactoferrin (Lf) is an 80 kDa non-heme Fe-binding glycoprotein of the transferrin family that is expressed in most biological fluids and is a major component of the mammalian innate immune system (Susana et al., 2009). Although the overall structure of Lf is very similar to that of transferrin they differ in their relative affinities for Fe and the propensity for release of Fe (Moore et al., 1997). The bovine Lf is a simple polypeptide chain comprised of 689 amino acid residues, and folded into 2 symmetrical lobes (N and C lobes), each of which is divided into 2 domains (Moore et al., 1997; Susana et al., 2009). Each lobe has a binding site for Fe³⁺ that lies between these 2 domains (Kurokawa et al., 1995). Furthermore, the Fe-binding sites comprise 4 protein ligands that provide 3 negative charges to balance the positive charge of Fe³⁺. Lactoferrin might be in an open conformation (Fe-free), or a closed one, as a Fe-saturated molecule (Baker & Baker, 2005). Additionally, bovine Lf binds Fe more weakly than human transferrin (Aisen & Leibman, 1972) and it releases Fe more readily (Legrand et al., 1990).

8.2 Functions

Several different functions have been attributed to Lf including regulation of cellular growth and differentiation, intestinal Fe homeostasis, and host defense against microbial infection and inflammation (Ward et al., 2002). In this review we will focus on the anti-microbial functions of Lf related to its function as an APP. Lactoferrin possesses several antimicrobial activities that contribute to the innate immune responses at the mucosal layers. Most bacterial pathogens are dependent on Fe for their metabolic activities, growth, and proliferation. Lactoferrin, by its Fe-binding capability, sequesters this essential metal affecting growth of Fe-requiring pathogenic bacteria including enteropathogenic *E. coli* (Brock 1980). Interestingly, removal of Fe favors the growth of bacteria with low Fe requirements such as lactic acid producing bacteria, which are beneficial to the host (Petschow et al. 1999). Antimicrobial activities have also been described for Lf, which are independent of the Fe status of the protein. In this regard, a direct bactericidal activity has been described for Lf, which is due to a cationic domain located in the N-terminus of the molecule (Bellamy *et al.* 1992). Recent findings indicate that Lf binds to surface molecules (receptors) expressed on many microorganisms, causing cell death. Most interestingly, it was shown that Lf prevents interaction between Gram-negative bacteria outer cell wall component LPS and cations like Ca²⁺ and Mg²⁺. The latter initiates the release of LPS from the cell wall, making bacteria vulnerable to external antimicrobial attacks (Coughlin et al., 1983; Ellison et al., 1988). Lactoferrin causes similar harm to Gram-positive bacteria based on its binding to anionic molecules on the bacterial surface, such as LTA, which subsequently decrease the negative charge on the cell wall favoring the contact between lysozyme and the underlying peptidoglycan over which it exerts an enzymatic effect (Leitch & Willcox, 1999). Lactoferrin aborts the viral infection at an early stage, by binding to certain viral antigens. This phenomenon is explained by binding of Lf to the glucosaminoglycans of eucaryotic cells; which prevents penetration of viral particles into cells (Yi et al., 1997). The protective effect of Lf is exerted by its suppression of major pro-inflammatory cytokines such as TNF α , IL-1 β , and IL-6 (Machnicki et al., 1993; Haversen et al., 2002), and in increasing the amount of anti-inflammatory IL-10.

8.3 Tissue distribution and factors that affect lactoferrin expression

8.3.1 Tissue distribution

Synthesis of Lf can be continuous as part of exocrine fluids, under control of hormones such as in the reproductive tract and mammary gland (Teng et al., 2002), or at certain stages of neutrophil differentiation (Masson et al., 1969). Lactoferrin is secreted in the apo-form from epithelial cells in most exocrine fluids such as saliva, bile, pancreatic and gastric fluids, tears, and milk (Montreuil et al., 1960). In milk, Lf is synthesized mostly by glandular epithelial cells; its concentration in humans may vary from 1-7 mg/mL (milk and colostrum). In bovine milk, average concentration of Lf is at 30 µg/mL. Prolactin has been shown to affect the amount of Lf synthesized in the mammary gland (Green & Pastewka, 1978), whereas estrogens affect its production in the reproductive mucosa (Pentecost & Teng, 1987; Walmer et al., 1992; Teng et al., 2002). Synthesis of Lf in the endometrium is influenced by both estrogens and epidermal growth factor (Nelson et al., 1991). In neutrophils, Lf is synthesized during their differentiation and is subsequently stored in specific granules, whereas in mature neutrophils the production of Lf ceases (Masson et al., 1969). During inflammation and disease conditions, concentration of Lf in biological fluids may increase greatly and constitute a potential biomarker of inflammatory states. This is particularly obvious in blood, where concentrations of Lf range from 0.4-2 µg/mL, under normal conditions, to 200 µg/mL during septicemia.

8.3.2 Lactoferrin in plasma, milk, and cervical mucus

Concentrations of Lf in milk vary from 0.1-1.0 mg/mL in healthy cows; however, it can rapidly increase in cows with sub-clinical and clinical mastitis and this concentration is positively correlated with SCC (Kawai et al., 1999; Hagiwara et al., 2003). Concentration of Lf is usually 100-fold greater during drying off and early mammary involution periods than during lactation (Kuttila et al., 2003).

Health status of the cows is a very important factor influencing the amount of Lf in the milk secretions. For example, Harmon et al. (1975) induced *E. coli* infection in a bovine mammary gland, which resulted in a 30-fold increase in the concentration of Lf in the mammary secretion, by 90 h post-inoculation. Furthermore, they observed that during acute mastitis, Lf levels in the milk increased up to 30-fold with the greatest production of Lf occurring in the infected quarter.

Concentrations of Lf in the cervical mucus of dairy cows range from 50 to 600 µg/mL, with a mean of 250 µg/mL (Rao et al., 1973). Interestingly, concentrations of Lf in the bovine and human cervical mucus are of the same order of magnitude. In samples collected from 7 women during mid-cycle, concentrations of Lf (Masson, 1970) ranged from 80 to 1,000 µg/mL with a mean of 350 µg/mL. Although it is not clear what is the source of Lf in the cervical gland it is likely that the cervical glands might secrete Lf in response to the bacterial presence in the reproductive tract.

Interestingly, a considerable variation in Lf content is also seen in the milk from different agricultural management systems. The concentration of Lf in the organic milk samples was found to be 0.03 mg/mL, or 1.5 times greater, compared to the 0.02 mg/mL in the conventional milk. The increased concentration of Lf in the organic milk is related to various factors like type of immunity boostings and other management interventions in organic dairy farms. Furthermore, a high concentration of Lf in organic milk strongly emphasizes the anti-microbiological functions of this APP in raw milk. It is well established that Lf

prevents the supply of Fe for pathogens, such as coliforms, thus inhibiting their growth and proliferation (Zagorska, 2007).

8.3.3 Age-and breed-related changes of lactoferrin in milk

Various studies have indicated that concentrations of Lf in different body fluids vary in relation with the gender and age of the animals (Bennett & Mohla, 1976; Bezwoda et al., 1985; Antonsen et al., 1993). For example, Tsuji et al. (1990) demonstrated that Lf content in the milk of 2 breeds of dairy cows (Holstein and Jersey) and 2 breeds of beef cattle (Japanese Black and Japanese Brown) was different among the breeds and cows of the same breed. They also showed that multiparous dairy cows had 2- to 3-fold greater Lf content in the colostrum than primiparous ones. The highest Lf content in the colostrum of dairy cows was observed in the second lactation; however, no differences were observed after the third lactation. Lactoferrin content among individual cows was variable, especially in dairy breeds. The highest concentration of Lf in milk was 11.77 mg/mL and the lowest was not detectable. Average Lf content in colostrum of dairy breeds was 2 mg/mL and in the colostrum of beef breeds was 0.5 mg/mL. The authors suggested that the reason for lower Lf content in the milk of beef cows is that they produce less milk than dairy cows.

8.4 Lactoferrin supplements against endotoxin-related diseases

Published studies indicate that the use of Lf as a supplement and its effects on immunity have been quite promising. When Lf is fed to adult animals and human infants, it increases markedly the beneficial microbiota such as *Bifidus* and decreases the number of pathogenic bacteria such as *E. coli*, *streptococcus*, and *clostridium* (Kruzel et al., 1998). In one study, administration of endotoxin in mice was associated with septic shock, whereas when mice were fed Lf the lethal effects of endotoxin subsided to a great extent (Zhang et al., 1999). In another study with baby piglets, Lf fed alleviated the severe effects of endotoxin when they were injected with *E. coli* and it was found that only 17 pigs died compared to 74 pigs in the control group (Lee et al., 1999). In addition, 2 human studies, using healthy human volunteers, demonstrated that ingestion of Lf, derived from cow's milk, had positive immunoregulatory effects. These effects were specific to each individual and were related to the initial profile of the immune system of each person. Those data suggested that cow's Lf might be used to improve the immune status of the patients (Zimecki et al., 1998). In another similar human study, it was demonstrated that administration of Lf influenced the primary activation of the host defense system (Yamauchi et al., 1998).

Moreover, Griffiths et al. (2004) examined the effects of oral supplementation of newborn Balb/c mice with *bifidobacteria* (*B. infantis*, *B. bifidum*) and Fe-free apo-lactoferrin (bovine and human) on gut microbial environment and endotoxin concentration in the ileocecal filtrates as well as mucosal immunity. They observed that oral administration of mice with *bifidobacteria* and/or apo-lactoferrin resulted in lower concentration of endotoxin compared to saline controls. These data suggest that Lf can also be used as a preventive tool against endotoxin-related diseases in other species including dairy cattle. In addition, since antimicrobial properties of Lf have been documented against both Gram-positive and Gram-negative bacteria Lf can be used against infections from those groups of bacteria (Sanchez et al., 1992; Chierici & Vigi, 1994). Lactoferrin content also varies considerably within breed. In beef breeds, half of the cows had values of Lf at nearly zero level (Tsuji et al., 1990).

9. Calcitonin gene-related peptide

9.1 Structure

Calcitonin gene-related peptide (CGRP) is a 37 amino acid neuropeptide generated by the splicing of the RNA transcript of calcitonin gene (Amara et al., 1982). By using NMR and distance geometry studies, Breeze et al. (1991) reported that CGRP sequence comprises an N-terminal disulfide bridge-linked loop between Cys2 and Cys7, followed by an alpha-helix in residues Val8-Arg18, and a poorly defined turn-type conformation between residues Ser19-Gly21. In a more recent study, an investigation conducted with NMR and molecular modeling techniques proposed a structure for CGRP characterized by a rigid N-terminal disulfide-bonded loop leading into helix segments between amino acids Val8-Leu16 compared to Val8-Arg18 and a gamma-turn between amino acids Ser19 and Gly21 (Boulanger et al., 1995). Two available isoforms of CGRP, from most species, have been reported including alpha-CGRP and beta-CGRP, derived from different genes (Amara et al., 1985). Both alpha- and beta-CGRP exhibit similar functional activities and differ with 1 and 3 amino acids from each other (Morris et al., 1984). The amino acid sequence of bovine CGRP shows a homology with other CGRPs identified so far. It is different by only 1 amino acid with rat alpha-CGRP and porcine CGRP and by 3 and 4 amino acids from human alpha- and beta-CGRP, respectively (Collyear et al., 1991).

9.2 Functions

Although CGRP is involved in multiple functions in various tissues including gastrointestinal, cardiovascular, respiratory, endocrine, and central nervous systems we will focus our review on the role of CGRP in the APR. In fact, CGRP was reported to be associated with the APR by Russwurm et al. (2001). Concentrations of CGRP in the plasma increase during sepsis and septic shock in humans (Joyce et al., 1990; Arnalich et al., 1995) and during endotoxemia in rats (Tang et al., 1997). A recent study of 61 patients with sepsis demonstrated that CGRP levels were greater in non-survivors than in survivors as early as day one of sepsis and remained increased in non-survivors throughout the entire disease state (Beer et al., 2002).

As an APP, CGRP may affect various metabolic, immunological, and biochemical processes of the host. For example, injection of CGRP in rodents is associated with increased concentrations of plasma glucose, lactate, and decreased plasma Ca (Young et al. 1993). Therefore, the increase of CGRP in plasma has been reported in various disease states, thus suggesting an important role of CGRP as a potential biomarker in predicting inflammatory conditions and diseases.

With regard to its immune roles CGRP was shown to stimulate eosinophil infiltration into tissues (Davies et al. 1992). Interestingly, CGRP also promotes adhesion of T cells to fibronectin, a glycoprotein component of the extracellular matrix, which plays a role in migration of T cells to the inflamed sites (Nong et al., 1989). Additionally, CGRP has been identified as a factor that inhibits capacities of macrophages to activate T-cells. It also prevents the inflammatory damage of the liver cells, inhibiting production of TNF- α (Kroeger et al., 2009). Besides its anti-inflammatory properties, recent data show that CGRP stimulates the release of pro-inflammatory cytokines. For example, exposure of BEAS-2B cell line to CGRP, at a range of concentrations, caused synthesis of IL-6, IL-8, and TNF- α 2 h after exposure and the release of their proteins 6 h after exposure (Veronesi et al. 1999).

Only a few studies have looked at the effects of CGRP in cows. In conscious hypophysectomized calves, this peptide caused a significant fall in adrenal vascular resistance and promoted steroidogenesis on the adrenal cortex in the absence of exogenous adrenocorticotrophin (ACTH) (Bloom et al., 1989). In fact, this experiment showed that CGRP produced a substantial rise in cortisol output, which rose steadily to a peak mean value of 409 pg/min/kg within 10 min, in the absence of exogenous ACTH.

9.3 Tissue distribution and factors that affect its release

9.3.1 Tissue distribution

To the best of our knowledge, there is no information about expression of CGRP in cattle tissues. Research in other species indicates that CGRP is highly expressed throughout the central and peripheral nervous systems and exhibits functional roles in various systems including gastrointestinal, cardiovascular, respiratory, endocrine, and central nervous (Brain & Grant, 2004). In another study in hamsters, infected with *E. coli* to cause sepsis, CGRP was expressed in multiple tissues including stomach, small intestines, colon, pancreas, heart, muscle, skin, visceral fat, testis, brain, spine, lungs, liver, kidneys, adrenal gland, spleen, white blood cells, peripheral macrophages, and thyroid glands versus expression only in thyroid glands, lungs, brain, colon, and spine in control animals (Domenech et al., 2001).

9.3.2 Disease states

There is a scarcity of data regarding the role of CGRP during inflammatory conditions in dairy cows and other ruminant species. In a study conducted by our team, to understand the etiology and pathogenesis of milk fever in dairy cows, we compared concentrations in the plasma of different variables including CGRP. Data from this study showed that dairy cows affected by milk fever had lower concentrations of CGRP in the plasma (38 vs 65 pg/dL) than control counterparts, and this effect was associated with lowered concentrations of Ca and P in the plasma (Ametaj et al., 2003). Interestingly, low plasma CGRP were associated with lowered concentrations of plasma Ca around calving date, particularly in the sick cows.

In another study conducted by us, in relation with the cause and pathology of fatty liver in dairy cows, we reported that cows with fatty liver had lower concentrations of CGRP in the plasma (ca. 20 pg/mL) throughout the study. On the other hand, cows that were not affected by fatty liver had greater concentrations of CGRP in the plasma on d 4 prepartum (45 vs 28 pg/mL) and during d 3, 8, 12, and 14 after calving. Moreover, concentration of plasma CGRP in control cows decreased by d 14 to levels similar to those observed in cows with fatty liver (ca. 25 pg/mL) and remained at that approximate concentration to the end of the study (Ametaj et al., 2005a,b). Although the functions of CGRP in dairy cows are not clear yet, it is possible that CGRP is involved in the metabolism of glucose and Ca in transition dairy cows. This hypothesis is supported by studies in rodents where injection of CGRP is associated with increased concentrations of glucose and lactate in the plasma (Young et al. 1993). Our data also demonstrated greater concentrations of glucose and lactate in the plasma of control cows, at several time-points, after parturition versus fatty liver cows. Interestingly, Hinshaw et al. (1974) reported that intravenous administration of glucose helped removal of TAG from the liver and lessened the lethal effects of endotoxemia. Indeed, in our study we found an inverse correlation between total lipids in the liver at d 8 and 12 after parturition and plasma CGRP, and with plasma glucose and

lactate at different postpartal times. These correlations raise the possibility that CGRP may help prevent fatty liver by increasing concentration and supply of glucose.

10. Ferritin

10.1 Structure

Ferritin was discovered in 1937 from horse spleen by French scientist Laufberger (1937), who coined the term “ferritin” from the Latin “ferratus” meaning “bound with Fe” after observation of the Fe content in the newly isolated protein (Laufberger, 1937). Ferritin is the principal Fe storage protein with 387-464 kDa. It contains a protein shell encasing an inner cavity where variable amounts of Fe are stored as a ferrihydrite mineral (Koorts & Viljoen, 2007). Structurally, a spherical protein coat of ferritin molecule, the apoferritin, surrounds an Fe core of hydroxyphosphate (Farrant, 1954). The apoferritin comprises 24 subunits that are composed of various combinations of 2 types of subunits, termed L (lever) and H (heart), having molecular weights of 19 and 21 kDa, respectively (Suryakala & Deshpande, 1999; Orino & Watanabe, 2008). The amount of core Fe ranges from 0 to 4,500 Fe atoms per molecule and reflects somatic Fe reserves, although naturally occurring ferritin contains less than 3,000 Fe atoms/molecule (Theil, 1987; Harrison & Arosio, 1996). Ferritin isomers vary with each other in terms of H to L subunits ratio depending on tissue type and developmental stage and in their metabolic properties (Wang et al., 2010). The H subunit contains the enzyme ferroxidase essential for incorporation of Fe, whereas the L subunit is devoid of ferroxidase and is primarily involved in Fe nucleation and physicochemical stability (Lawson et al., 1991; Levi et al., 1992). Serum ferritin is composed primarily of the L subunit type and relatively poor in Fe, whereas the ratio of H/L subunits ranges from 0.03 to 0.27 (Kakuta et al., 1997).

Ferritin from cattle contains a major and a minor protein band, which contains high aspartate, glutamate, and glycine and lower methionine and histidine (Suryakala & Deshpande, 1999). Furthermore, bovine ferritin has comparatively higher concentrations of proline, threonine, and valine than equine or human ferritins (Cetinkaya et al., 1985). Although sequence identities of amino acids between mammalian ferritin H and L subunits are relatively low (50–56%), they are highly conserved among the corresponding subunits (H: 88–99%; L: 78–92%; Orino & Watanabe, 2008). $\text{PO}_4^{(-3)}/\text{Fe}$ ratio of 0.26 and two values of 16.9 and 10.8 S20w were noted for bovine liver ferritin (Suryakala & Deshpande, 1999). Additionally, ferritin molecule contains 20% neutral carbohydrates. Iron content of liver protein is 9.58% in cattle and the Fe:protein ratio of bovine ferritin has been reported to be at 0.161 (Suryakala & Deshpande, 1999). Using quantitative immunoprecipitation techniques concentration of Fe in serum ferritin was from 0.16 to 0.96 mg/mL (Suryakala & Deshpande, 1999), and the Fe content of ferritin was at 20%, regardless of its protein concentration in bovine fetal sera (Kakuta et al., 1997). For measurement of serum ferritin, antibody-driven reactions such as radioimmunoassay or enzyme linked immunosorbent assay (ELISA) are the commonly used assays. The purified ferritin from cattle liver cross-reacts with anti-buffalo liver and anti-equine spleen ferritins (antisera) by immunogel diffusion and immunoelectrophoresis (Suryakala & Deshpande, 1999).

10.2 Functions

Different studies have shown that extracellular ferritin can function as an Fe transporter to provide Fe to various cells (Wang et al. 2010). Sibille et al. (1988) calculated that one Kupffer

cell could accumulate over 160,000 Fe molecules/minute via an efficient carrier mechanism. Moreover, ferritin plays a major role in intracellular Fe storage (Harrison et al., 1986). The survival of a bacterium within a host depends on its ability to extract nutrients from surrounding environment. Indeed Fe is an essential component or cofactor of many enzyme systems in bacterium, hence, it is a very important nutrient for bacteria to survive. However, because of its hydrophobic nature, most of the Fe in the host tissues is bound to high-affinity binding proteins like transferrin and lactoferrin while free Fe is very low (at 10^{-18} M). To scavenge Fe from these binding proteins, bacteria have evolved various kinds of highly developed and efficient mechanisms. For example, some highly virulent bacteria, such as *E. coli* and *Klebsiella* species, secrete siderophores or siderochromes, which serve as high affinity extracellular Fe chelating molecules. Similarly, mycobacteria produce mycobactin and exochelin, both Fe-binding proteins, to acquire Fe from the environment (Momotani et al. 1986). Other species of bacteria express receptors for transferring lactoferrin on their surfaces and internalize Fe this way. Still few others extract bounded Fe by proteolytic cleavage. In response to bacterial infection, host antimicrobial defense mechanisms involve sequestration of Fe away from the pathogens (Squires, 2004; Kannon, 2006). To make a host's internal environment more hostile to an invading microorganism, pro-inflammatory cytokines such as IL-1 β inhibit synthesis of hepatic transferrin concurrently stimulating synthesis of ferritin in various cells throughout the body (Rogers et al., 1990). Interestingly, Gray et al. (2002) found activation of regulatory T cells by H ferritin subunit, resulting in IL-10 production. Similarly, TNF- α induces ferritin secretion in cultured human hepatocyte (Torti & Torti, 2002). The overall result is a redistribution of Fe from extracellular to intracellular compartments, thus rendering Fe less accessible to invading pathogenic bacteria (Squires, 2004; Kannon, 2006).

Superoxide radicals (O_2^-), produced by enhancement of mitochondrial cytochrome P450 by toxins or pro-oxidants, or NADPH oxidase by phagocytes (Vignais, 2002), play key roles in oxidative stress by releasing Fe^{2+} from ferritin after donating an electron to Fe^{3+} (McCord, 1996; Orino & Watanabe, 2008). Oxidative stress mediated by reactive oxygen species (ROS) is major factor which is directly linked to inflammatory, malignant, and metabolic diseases in domestic and farm animals (Orino & Watanabe, 2008). However, oxidative stress mediated damage depends on the level of cellular Fe content, cell type, and total body Fe status because through the Fenton reaction an excess Fe^{2+} pool produces the most harmful free radicals (i. e., hydroxyls). There is an emerging body of evidence indicating that ferritin plays a protective role against oxidative stress. For instance, mouse ferritin H or L subunits are over-expressed in HeLa cells, and this lowers production of cellular ROS by pro-oxidants (Orino et al., 2001; Orino & Watanabe, 2008).

10.3 Tissue distribution and factors that affect its expression

10.3.1 Tissue distribution

Ferritin is widely distributed in almost each system of the body, which includes blood, spleen, liver, kidney, bone marrow, heart, pancreas, intestines, and placenta although its concentration is comparatively greater in the liver, spleen, and bone marrow (Harrison et al., 1986; Cetinkaya et al., 1985; Suryakala & Deshpande, 1999). Ferritin is distributed intracellularly in cytosol, mitochondria, and nucleus (Cai et al., 1997; Levi & Arosio, 2004; Surguladze et al., 2005); however because of the water-soluble nature, a small amount leaks into the extracellular fluid (Orino & Watanabe, 2008). In the circulatory system, it generally circulates in relatively low concentrations, at $< 1 \mu\text{g/mL}$. Circulating ferritin can be

classified into two types: (1) serum ferritin, of which the source and secretion mechanisms remain to be elucidated, and (2) tissue ferritin, which probably leaks from damaged tissues (Orino & Watanabe, 2008). Ferritin is also isolated from other extracellular fluids, such as synovial fluid (Ota & Katsuki, 1998) and milk (Orino et al., 2004). Most of the serum ferritin remains in equilibrium with tissue ferritin, and it is directly proportional to Fe stores under normal conditions. The percentage of ferritin Fe to total serum Fe ranges from 8.8 to 28.5% in bovine fetus (Kakuta et al., 1997). Concentration of ferritin in the serum increases markedly with Fe supplementation in calves (Miyata et al., 1984). In cattle, various studies have shown that the normal concentration of serum ferritin ranges between 33-55 ng/mL (Smith, 1997). Moreover, serum ferritin levels between 10-30 ng/mL indicate Fe deprivation, whereas those of more than 80 ng/mL suggest Fe overload (Suttle, 2010)

10.3.2 Stage of lactation, breed, and age

Furugouri et al. (1982) reported that from a relatively baseline concentration during late gestation (35 ng/mL), ferritin gradually increases starting at 3 d prepartum and reaches its peak level at 2 wk postpartum (75 ng/mL). Subsequently, up to 10 wk postpartum it declines gradually, and thereafter remains almost unchanged (40 ng/mL). Although, concentration of ferritin in the serum is associated with gender in humans (Urushizaki, & Kohgo, 1980), no such differences are recorded in cattle (Miyata & Fourgouri, 1984; Atyabi et al., 2006), which might be attributed to absence of menstruation and blood loss in cows. On the other hand, serum ferritin in calves is as low as 14 ng/mL during the first wk and rises to 33 ng/mL at 1 mo of age; however, no further change is observed up to 25 mo of age (Miyata & Furugouri et al., 1987). Grazing has also been reported to be associated with serum ferritin concentration in cattle (Miyata et al., 1986). There are no studies in cattle to show an effect of breed and parity on concentrations of serum ferritin, however, such differences among human races and an inverse relationship between human parity and serum ferritin has been reported (Lazebnik et al., 1989).

Synthesis of ferritin is controlled at both transcriptional and translational levels. In fact, this is regulated by Fe, at a translational level through interaction between Fe regulatory protein and conserved Fe responsive element (IRE, 28 bp) in the 50-untranslated region of ferritin H and L subunit mRNAs (Klausner & Harford, 1989; Torti & Torti, 2002; Orino & Watanabe, 2008). Contrary to this well-defined regulatory mechanism, transcriptional regulation of ferritin gene by oxidative stress (Wasserman & Fahl, 1997; Tsuji et al., 2000), cytokines (Torti et al., 1988; Wei et al., 1990), oncogenes (Tsuji et al., 1993), and hormones (Yokomori et al., 1991; Leedman et al., 1996) is Fe-independent and less evident (Orino & Watanabe, 2008).

10.3.3 Ferritin during disease states

Serum ferritin is a true indicator of Fe-deficiency anemia and is reflected by lower than normal concentration of serum ferritin. Increased serum ferritin suggests pathologies associated with increased storage of Fe such as hemolytic anemia, megaloblastic anemia, or anemia of chronic disease in animals. Similarly, concentration of ferritin in the serum gradually increases with advancement of anemia in calves infected with *Theileria sergenti*. Serum ferritin also is increased during hepatic disease and neoplastic disorders (Roperto et al., 2010). Interestingly in steers fed a diet with lower calories there was an increase of serum ferritin within a 5 mo period (Furugouri, 1984). Underfeeding in cattle has been reported to lower hepatic glucose-6-phosphate dehydrogenase and superoxide dismutase activities, which result in depletion of antioxidant defense mechanisms and eventually give rise to a

state of oxidative stress and peroxidation. Serum ferritin is overproduced in conditions such as uncontrolled cellular proliferation, excessive production of toxic oxygen radicals, and during infectious and inflammatory states (Orino & Watanabe, 2008). Increased circulatory ferritin, during those states, reflects elevated total body Fe storage; however, these stores are sequestered and are not available for hematopoiesis, a process, which contributes to the widely recognized anemia of inflammation (Wang et al., 2010). Practical implication of measurement of serum ferritin is to differentiate between true Fe deficiency (ferritin decreases) from the anemia of inflammation (ferritin is normal or increases). It is worth mentioning that true Fe deficiency could be missed if serum ferritin is elevated by a concomitant inflammatory condition. For example, concentration of ferritin is not recommended as a marker for the size of Fe stores in the early stages of lactation due to inflammation that accompanies parturition (Furugouri et al., 1982). Thus, it is imperative to monitor serum ferritin in association with other APP (Smith, 1997).

The study of Orino et al (2004) showed that ferritin in the bovine milk is an indicator of intramammary infection as the concentrations of ferritin in the milk of mastitic cows (134.2 ± 28.7 ng/mL) were significantly greater than those of non-infected lactating cows (7.2 ± 1.2 ng/mL). The latter authors suggested that serum ferritin is an indicator of disease status and also may be a prognostic indicator of the disease (Orino & Watanabe, 2008).

11. Conclusions

Research on APP in cattle started several decades ago and the number of publications during the last 5-10 years has increased noticeably. There is an increasing body of evidence to support utilization of APP as biomarkers of inflammation in cattle. Different investigators have reported enhanced concentrations of APP in various metabolic and infectious diseases including fatty liver, milk fever, downer cow syndrome, milk fat depression, mastitis, metritis, laminitis, grain-induced ruminal acidosis and several infectious and viral diseases. However, it's more appropriate to conclude that APP might be used to indicate a general inflammatory state in the host and not a specific disease. Therefore, increased presence of APP in various fluids of the host should be used to suggest breaching of immune barriers of the host by bacterial, viral, fungal cells or their toxic products. Several APP have just begun to be tackled by bovine researchers; however, more research is warranted to establish the role(s) that APP play in host innate immunity.

12. Acknowledgment

We acknowledge the financial support of different funding organizations that have supported our research activities in the area of innate immunity during the last 8 years including Alberta Livestock Industry Development Fund, Alberta Livestock and Meat Agency, Alberta Milk, and National Science and Engineering Research Council of Canada.

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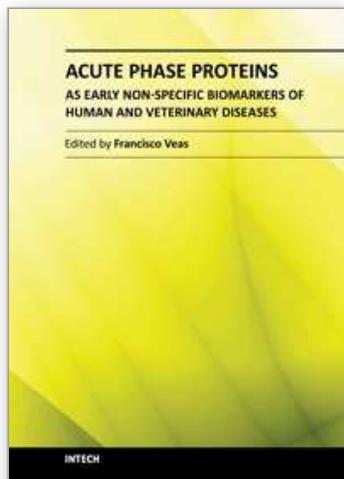
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Edited by Prof. Francisco Veas

ISBN 978-953-307-873-1

Hard cover, 408 pages

Publisher InTech

Published online 10, October, 2011

Published in print edition October, 2011

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