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# Immune components of bovine colostrum and milk<sup>1</sup>

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**ABSTRACT:** Colostrum and milk provide a complete diet for the neonate. In ruminants, colostrum is also the sole source of initial acquired immunity for the offspring. Milk therefore plays an important role in mammalian host defense. In colostrum, the concentration of immunoglobulins is particularly high, with IgG being the major immunoglobulin class present in ruminant milk, in contrast to IgA being the major immunoglobulin present in human milk. Immunoglobulins are transported into mammary secretions via specialized receptors. In addition to immunoglobulins, both colostrum and milk contain viable cells, including neutrophils and macrophages, which secrete a range of immune-related components into milk. These include cytokines and antimicrobial proteins and peptides, such as lactoferrin, defensins, and cathelicidins. Mammary epithelial cells themselves also contribute to the host defense by secreting a range of innate immune effector molecules. A

detailed understanding of these proteins and peptides offers great potential to add value to the dairy industry. This is demonstrated by the wide-ranging commercial applications of lactoferrin derived from bovine milk. Knowledge of the immune function of milk, in particular, how the gland responds to pathogens, can be used to boost the concentrations of immune factors in milk through farm management practices and vaccination protocols. The latter approach is currently being used to maximize yields of bovine milk-derived IgA directed at specific antigens for therapeutic and prophylactic use. Increasingly sophisticated proteomics technologies are being applied to identify and characterize the functions of the minor components of milk. An overview is presented of the immune factors in colostrum and milk as well as the results of research aimed at realizing this untapped value in milk.

**Key words:** colostrum, cow, immune, mammary gland, milk

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## INTRODUCTION

The mammalian neonate is unable to collect, chew, or digest solid food, relying entirely on the colostrum of its mother and subsequently on milk for its survival. In addition to providing a complete diet with all the essential nutrients for the neonate during the initial phase of its life, colostrum also provides essential immunological protection. In ruminants in particular, for which no exchange of immune factors occurs in utero, colostrum and, to a lesser extent, milk provide protection through a high immunoglobulin content, without which the ruminant would not survive (Larson et al., 1980). The colostrum immunoglobulins, in conjunction with the ability of the ruminant neonatal gut to allow unrestricted passage of the large immunoglobulin molecules,

provide the young animal with passive immunization. However, both the concentration of immunoglobulins in colostrum and the permeability of the gut decrease rapidly and progressively over the first 48 h after birth (Bush and Staley, 1980; Moore et al., 2005). Therefore, an adequate supply of colostrum, with abundant immunoglobulins, is essential during this brief period of time for the young to gain sufficient passive immunity to be able to survive until its own immune system is fully developed.

Immune factors in colostrum and milk also play an important role in the host defense of the mammary gland itself, protecting it from pathogenic organisms (Sordillo et al., 1997; Oviedo-Boyso et al., 2007). The mammary gland is very susceptible to infection because mammary secretions provide an excellent source of nutrients for pathogens, the body temperature is ideal for bacteria growth, and the gland, via the teat opening, has a direct link to the external environment. The mammary host defense system has evolved into an extremely well-developed, complex, and highly effective barrier against pathogens, integrating both the innate and acquired immune response.

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**Table 1.** Immunoglobulins in bovine and human colostrum and milk<sup>1</sup>

Species	Immunoglobulin	Concentration, mg/mL		% of total immunoglobulins	
		Colostrum	Milk	Colostrum	Milk
Bovine	IgG <sub>1</sub>	47.60	0.59	81.0	73.0
	IgG <sub>2</sub>	2.90	0.02	5.0	2.5
	IgA	3.90	0.14	7.0	18.0
	IgM	4.20	0.05	7.0	6.5
Human	IgG	0.43	0.04	2.0	3.0
	IgA	17.35	1.00	90.0	87.0
	IgM	1.59	0.10	8.0	10.0

<sup>1</sup>From Butler (1973).

Immune components in milk are important to all young mammals, including humans. Newburg (2005) recently provided an excellent overview of immune components in human milk, and Wheeler et al. (2007) presented a comprehensive historical review of the discovery and importance of immune factors in milk. The present review mainly focuses on immune components in bovine colostrum and milk but draws on data from other species. In addition, in this review we discuss several commercial applications based on the exploitation of the bovine mammary immune system.

## COLOSTRUM AND MILK IMMUNE COMPONENTS

### *Mammary Immunity*

Both the adaptive or acquired immune system and the innate immune system operate in the bovine mammary gland. The adaptive immune response is mediated by T and B cells and relies on memory to respond quickly to threats to which it has previously been exposed. However, it is slow to respond to novel threats to which it has not previously been exposed. In contrast, the innate immune system is the first line of defense protecting the body from infectious pathogens before the adaptive immune system comes into play. It represents a complex interaction of cellular and molecular processes aimed at detecting and subsequently eliminating harmful pathogens. The innate immune system of the bovine mammary gland has evolved into a highly effective host defense mechanism (Rainard and Riollet, 2006). It has even been postulated that the mammary gland itself may be an extension of the innate immune system (Vorbach et al., 2006). The mammary epithelial cells (**MEC**) themselves play a key role in the innate immune response. They express a range of pathogen recognition receptors, most notably the Toll-like receptors (**TLR**), which recognize specific molecular motifs (pathogen-associated molecular patterns, or **PAMP**) on the surface of pathogens. Activation of these receptors initiates a signaling cascade in which nuclear factor- $\kappa$ B plays a pivotal role in coordinating multiple signals and directing expression of effector response genes (Akira and Takeda, 2004). Both the acquired and innate immune systems facilitate the constitutive or

acute transient presence of a wide range of immune-related components in colostrum and milk.

### *Immune Components Related to the Acquired Immune System*

Immunoglobulin antibodies are the main immune components of the acquired immune system present in colostrum and milk. The most abundant immunoglobulin class in bovine milk and colostrum is IgG<sub>1</sub> (Barrington et al., 1997). In contrast, IgA and IgM are present at much reduced concentrations in bovine colostrum and milk (Table 1). Of note are important differences in the abundance of different immunoglobulin classes in colostrum and milk among species; IgA is the predominant immunoglobulin in human mammary secretions (Table 1).

The bovine mammary gland plays an active role in regulating the concentration of the different immunoglobulins present in colostrum and milk, although the mammary epithelium itself does not synthesize immunoglobulins. Whereas a small amount of the immunoglobulins may enter colostrum and milk from the blood serum via the paracellular route as a result of “leaky” intercellular tight junctions (Lacy-Hulbert et al., 1999), the vast majority of immunoglobulins enter via a selective receptor-mediated intracellular route. These immunoglobulins may be blood-derived or produced in situ by intramammary plasma cells. The presence of a specific IgG receptor (neonatal Fc receptor) in MEC has been reported for several eutherian mammals and marsupials, including possums and pigs (Adamski et al., 2000; Schnulle and Hurley, 2003). Recently, Mayer et al. (2005) showed that this receptor plays an active role in transporting IgG into the lactating bovine mammary gland. The IgA found in bovine colostrum and milk is produced by resident intramammary plasma cells. These plasma cells traffic to the mammary gland via the blood, where their uptake is mediated by locally produced chemokines (Wilson and Butcher, 2004). The translocation of IgA across the MEC is facilitated by the polymeric immunoglobulin receptor (**pIgR**) expressed on the mucosal epithelium. At the apical side of MEC, pIgR is cleaved and IgA is released into the alveolar lumen along with a portion of pIgR, secretory compo-

ment (SC; Apodaca et al., 1994). The expression and regulation of receptors involved in mammary IgG and IgA transport in ruminants appear to be regulated by endocrine changes around the time of parturition (Barrington et al., 2001; Rincheval-Arnold et al., 2002).

The highly glycosylated polypeptide SC is another immune factor present in colostrum and milk that interacts with the adaptive immune system. Secretory component derived from a portion of the IgA receptor not only enhances IgA functionality when it is attached to IgA (Phalipon et al., 2002), but may have direct protective properties itself. Motegi and Kita (1998) showed that SC enhanced the effector function of eosinophils, indicating a possible role in the regulation of mucosal tissue inflammation. Moreover, SC can act as a microbial scavenger. Isolated from human colostrum, SC was shown to bind enteropathogenic *Escherichia coli*, protecting epithelial cells from bacterial invasion and adherence (Perrier et al., 2006).

### *Immune Components Related to the Innate Immune System*

A wide variety of components linked to the innate immune response have been identified in colostrum and milk. These include neutrophils, macrophages, complement, oligosaccharides, gangliosides, reactive oxygen species, acute-phase proteins, immunomodulatory factors (including many different pro- and anti-inflammatory cytokines), ribonucleases (**RNase**), and a range of peptides and proteins with direct antimicrobial activity (Gopal and Gill, 2000; Rainard and Riollot, 2006; Oviedo-Boyso et al., 2007; Leitner et al., 2008). Many of these components originate from specialized cells that traffic to the mammary gland. For example, neutrophils and macrophages infiltrating the mammary gland not only kill bacteria directly through phagocytosis, but are also responsible for the production of many cytokines, reactive oxygen species, and antimicrobial peptides. Several recent reports surveying the minor constituents of milk from healthy and infected glands have noted the predominance of host defense-related proteins (Palmer et al., 2006; Rainard and Riollot, 2006; Smolenski et al., 2007; Wheeler et al., 2007; Singh et al., 2008). However, it is beyond the scope of the current overview to discuss in detail the role and mechanisms of action of all the innate immune factors that have been described in colostrum and milk.

The bovine mammary epithelium itself also plays an active role in host defense and synthesizes several innate immune factors, such as lactoferrin (Sanchez et al., 1992),  $\beta$ -defensin (Swanson et al., 2004), and lipopolysaccharide-binding protein (Miles, 2004). Moreover, preparations of the membranes surrounding the milk fat globules secreted by MEC, which originate from the apical membrane of the MEC, contain many peptides, proteins, and lipids that are involved in host defense (Sprong et al., 2001; Smolenski et al., 2007). Key milk fat globule membrane components, such as

xanthine oxidase and sphingolipids, have antibacterial activity against a range of bacteria (Sprong et al., 2001; Hancock et al., 2002).

## FACTORS AFFECTING IMMUNE COMPONENTS IN MILK AND COLOSTRUM

### *Animal Factors*

The presence and concentrations of immune components in milk vary depending on the stage of lactation. Immediately postpartum, high concentrations of immune components can be found in colostrum, with immunoglobulins making up approximately 5% of the colostrum content (Table 1). Subsequently, immunoglobulin concentrations decrease significantly, but increase again during late lactation (Auldust et al., 1998). Similarly, the number and proportion of neutrophils in milk increase sharply toward the end of lactation (Rainard and Riollot, 2006). The content of innate immune proteins in milk also varies with the stage of lactation. The concentration of lactoferrin is least at peak lactation and progressively increases as lactation advances (Cheng et al., 2008), whereas that of lactoperoxidase appears to be more cyclical in nature, with peaks and troughs throughout lactation (Fonteh et al., 2002).

The concentration of immune components in milk varies considerably among healthy cows. In milk samples collected from a herd of 189 healthy cows, there was more than a 20-fold difference in the lactoferrin concentrations (Figure 1). Similarly, there were large differences in the concentrations of lactoperoxidase in the milk of individual goats and cows (Fonteh et al., 2002). Such a significant disparity among animals indicates an opportunity to select for those high in milk immune factors and establish special herds for commercial exploitation.

### *Mastitis*

Mastitis is an inflammation of the mammary gland, predominantly caused by pathogenic bacteria. It is therefore not surprising that mastitis will result in an acute upregulation of the immune system, in particular, the innate immune system (Oviedo-Boyso et al., 2007). As a result, a rapid transient increase in immune components in milk can be observed.

The presence of pathogenic bacteria is sensed by MEC and macrophages through the interaction of components (i.e., PAMP) with one or more receptors, most notably the TLR. Of the known TLR, only TLR2 and TLR4 are known to be expressed in bovine MEC. After the recognition of PAMP by TLR or alternative recognition pathways, a rapid and complex innate immune cascade is initiated. Key to this process is the ability of the MEC and macrophages present in milk to initiate an inflammatory response by secreting proinflammatory cytokines and chemokines, such as tumor necrosis

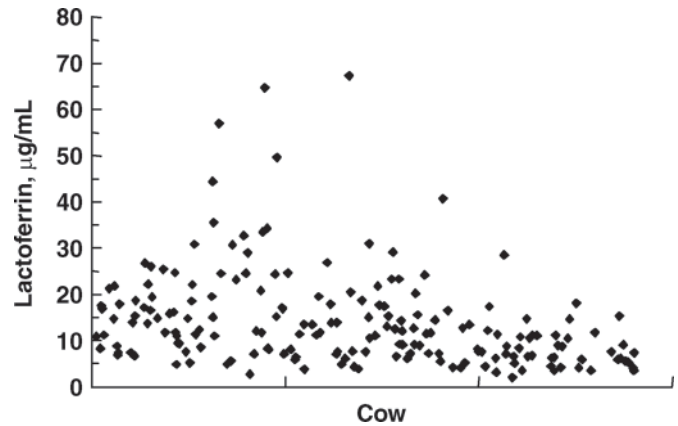
factor- $\alpha$ , IL-1 $\beta$ , and IL-6, to recruit neutrophils to the mammary gland (Oviedo-Boyso et al., 2007). In addition, the concentrations of antimicrobial peptides and proteins such as lactoferrin,  $\beta$ -defensin, cathelicidins, and lysozyme in milk are increased rapidly (reviewed by Wheeler et al., 2007). The exact expression profile of these upregulated immune components depends, however, on the specific causative pathogen, with clear differences in the type of immune component and timing of its regulation between different bacterial species (Griesbeck-Zilch et al., 2008). If the innate immune response is unable to contain the infection, then the adaptive immune system will come into play via T and B lymphocyte responses. Lately, it has been increasingly recognized that the innate and acquired immune systems do not operate independently, but interact in a complex, cytokine-facilitated manner when controlling an infection.

### *Farm Management Practices*

Farm management practices may affect the concentration of immune components in milk. Unhygienic practices during the milking process will increase the incidence of bacterial challenge in the mammary gland, which in turn will elicit a strong immune response, as discussed previously. A common strategy for the entire lactation or part of the lactation in low-input dairying systems is to change the milking frequency from twice daily to once daily (Clark et al., 2006). This results in a mild mammary inflammatory response, resulting in leaky tight junctions between MEC (Stelwagen et al., 1995). This increase in paracellular permeability has been shown to result in a significant increase in both cellular (i.e., IgG) and innate (i.e., neutrophils) components in milk (Stelwagen and Lacy-Hulbert, 1996; Lacy-Hulbert et al., 1999). Moreover, the concentration of lactoferrin in milk was shown to double after only 3 d of once-daily milking compared with twice-daily milking (Farr et al., 2002). Angiogenin (or RNase5), shown to have both antimicrobial activity (Hooper et al., 2003) and RNase activity (Shapiro et al., 1986), was also increased in bovine milk with once-daily milking (K. Stelwagen, M. K. Broadhurst, K. Kim, A. M. Molenaar, D. P. Harris, and T. T. Wheeler, Dairy Science and Technology, AgResearch Ltd., Hamilton, New Zealand, unpublished results).

## **APPLICATIONS OF IMMUNE COMPONENTS TO ADD VALUE TO MILK**

Milk production by the modern dairy cow is far in excess of the nutrient requirements of its calf, and milk has become a significant economic commodity. Traditionally, milk has been used by humans for direct consumption or as a raw ingredient for manufacturing cheese, butter, fermented dairy products, or milk powder. However, recent proteomic studies of human colos-



**Figure 1.** Lactoferrin concentration in milk of healthy cows ( $n = 189$ ) in a commercial New Zealand dairy herd during early lactation (57 d in milk; K. Stelwagen, unpublished data).

trum (Palmer et al., 2006) and bovine milk (Smolenski et al., 2007) have revealed a large number of minor components, many of which have an immune function. Such immune components hold great potential to add significant value to milk, with applications in pet food, cosmetics, personal care, and health promotion (Horton, 1995; Wakabayashi et al., 2006).

### *Innate Immune Antimicrobial and Immunomodulatory Factors*

Small cationic peptides and proteins of the innate immune system are increasingly valued for their potential as antibacterial, antifungal, or antiviral products, or their combination (Christoffersen, 2006; Sheridan, 2006). They may even hold potential as natural alternatives to traditional antibiotics, because the development of resistance may be less of a problem with such innate molecules (Zasloff, 2002). Several antimicrobial molecules are currently at various stages of development by several biotechnology companies (Zasloff, 2002; Sheridan, 2006). Although such antimicrobials could be extracted from a wide range of biological sources, including plants, insects, and marine organisms (Sheridan, 2006), milk lends itself particularly well to mining such components. Milk can easily be harvested in liquid form, it is already processed on a large scale by dairy manufacturers, and, importantly, it contains many immune components.

Milk-derived lactoferrin was one of the first immune components of milk to be commercially extracted for its antimicrobial and antiviral properties. It can be found as a valuable ingredient in infant formula and other foods for both human and pet consumption, in skin care products (e.g., cosmetics), and in oral care products such as toothpaste, mouthwash, and chewing gum (Horton, 1995; Wakabayashi et al., 2006). Lactoferrin, in combination with lactam antibiotics, also shows promise in the treatment of bovine mastitis (Komine et al., 2006; Petitclerc et al., 2007). Lactoperoxidase, another antimicrobial protein commercially extracted



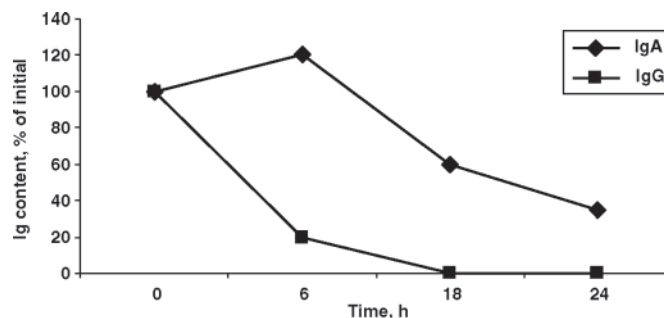
from milk, is used for food preservation, oral care, and even as a plant fungicide (Horton, 1995; Boots and Floris, 2006). The lytic enzyme lysozyme, which is present in milk, also has application as a food preservative in the food industry (Nattress and Baker, 2003).

Despite the commercial application of some milk-derived immune components to date, the commercial potential of the majority of immune-active components identified in milk remains untapped. Many of these components have activities that are not directly antimicrobial. Instead, they contribute to the generation of a robust and appropriate immune response through such mechanisms as the detection of pathogens, the recruitment of immune cells such as neutrophils, the promotion of phagocytosis and cell-mediated killing, activation of complement pathways, and controlled resolution of inflammation (Mookherjee and Hancock, 2007). The extraction of such components could provide a new class of milk-derived, immune-related bioactive compounds that prevent infection or promote the resolution of disease by directly modulating the host immune response. The development of such immunomodulatory bioactive compounds does pose challenges. In particular, the host immune response is a fine balance between pro- and anti-inflammatory components, and manipulating this response requires care. However, these bioactive compounds do offer powerful strategies for preventing or treating disease that are not dependent on antibiotics and the associated difficulties of antibiotic resistance. Given the range of soluble immune active components that have now been characterized in milk and their ease of extraction, it is likely that some of these proteins will form the basis for future products and treatments that directly modulate the host immune systems of humans or production animals.

### Hyperimmune Milk

Boosting the natural concentrations of immune components in colostrum and milk through vaccination of cows offers great potential for their use as prophylactic or therapeutic products in humans. Cows are vaccinated with an antigen that is appropriate for the condition to be treated. The best-known commercial example of such hyperimmune milk is the range of Stolle products (Stolle Milk Biologics Inc., Cincinnati, OH). The Stolle protocol involves biweekly vaccination of lactating cows with a multivalent killed bacterial antigen, resulting in an elevated IgG response in the milk. This milk has demonstrated antiinflammatory activity, mediated by tight junction-regulated suppression of neutrophil emigration from the vasculature (Ormrod and Miller, 1992; Stelwagen and Ormrod, 1998).

Hyperimmune colostrum from cows vaccinated with human rotavirus was an effective therapeutic in reducing the duration and severity of rotavirus-caused diarrhea in a double-blind controlled clinical study with infants of 6 to 24 mo of age (Mitra et al., 1995). Moreover, prophylactic treatment with *Cryptosporidium parvum*



**Figure 2.** Stability of IgA and IgG from ovine colostrum after in vitro incubation at 37°C in the presence of the small intestinal content of 6-d-old lambs (Willix-Payne et al., 2001).

hyperimmune colostrum in healthy volunteers significantly reduced oocyst excretion after parasite challenge and further tended to reduce diarrhea (Okhuysen et al., 1998). Although these and other studies show the great potential of hyperimmune milk products, these products are not always effective (Tacket et al., 1999). Variability in the effectiveness of hyperimmune colostrum and milk may be related to the fact that the majority of these studies are based on an elevated IgG response in the bovine colostrum and milk. However, it was demonstrated that IgA is the most common and stable immunoglobulin in human milk (Table 1 and Figure 2). In our laboratory, we have developed a proprietary procedure to produce hyperimmune bovine colostrum and milk with significantly elevated concentrations of antigen-specific IgA (Hodgkinson and Hodgkinson, 2003). The added benefit of this procedure is that cows are vaccinated only during the dry period, with elevated IgA titers remaining during the entire subsequent lactation. Using this procedure, Hodgkinson et al. (2007) showed that a hyperimmune milk protein concentrate effectively prevented adherence of the yeast *Candida albicans* on a tooth surface model. Collectively, these studies on the use of hyperimmune colostrum and milk demonstrate great potential for the prophylactic treatment, therapeutic treatment, or both of adverse infective conditions in humans.

### Summary and Conclusions

Bovine colostrum and milk are rich sources of immune components that are contributed by both the acquired and innate immune systems. These immune factors play a role in conveying passive immunity to the offspring and protective host immunity of the mammary gland itself. Variability in immune components in colostrum and milk are due to animal factors and management factors. Increasingly, immune components from colostrum and milk are being exploited commercially as antimicrobial agents. Moreover, vaccination procedures to boost the natural concentrations of immune components offer great potential in the development of hyperimmune milk-derived products for prophylactic or therapeutic use in humans.

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