Bovine Collectins: Role in Health and Disease

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Introduction

The management of infectious diseases in cattle (*Bos taurus*) is of key importance for the economic well-being and maintenance of the agricultural and food industries worldwide, affecting both cattle breeding, meat and milk production. Common infectious diseases include mastitis, bovine respiratory disease (RBD), bovine tuberculosis, gastrointestinal disease, which account for significant economic burden and some other bovine zoonoses (Miles 2009; Abernethy et al. 2013; APHA 2020; Mcdaniel et al. 2014). Furthermore, the prevalence of infectious diseases is also a major cause of increased agricultural antibiotic use, which increases the risk of anti-microbial resistance (Prescott et al. 2012). Therefore, a greater emphasis should be placed on understanding the immunobiology of *Bos taurus*, particularly genetic deficiencies that contribute to infectious disease susceptibility but also immunological mechanisms that could potentially augment protection against these diseases without the requirement of anti-microbials.

As in all mammals, the bovine innate immune system is the first-line defence against pathogens and a major component of this are a group of proteins called collectins. Collectins are a family of proteins that have calcium (Ca^{2+}) dependent activity and similar structures characterised by a carbohydrate recognition domain (CRD) linked to collagen-like region through an alpha-helical coiled-coil neck region. They have diverse roles in innate immune defence and normal physiology. The bovine collectins comprise of two lung proteins: surfactant protein A (SP-A) and surfactant protein D (SP-D), a number of serum proteins, mannan-binding lectin (MBL), conglutinin (CGN), collectin of 43 kDa (CL-43), collectin of 46 kDa (CL-46) as well as two recently discovered collectins: collectin liver 1 (CL-L1) and

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collectin placenta 1 (CL-P1). The collectins are present in all mammals, except for CGN (CGN), which seems to be unique to *Bovidae* (Lu et al. 1993a).

The collectins can form several higher order structures. The N-terminal regions have 1–3 cysteine residues that can form disulphide links, cross-linking the collagen regions, which are comprised of three polypeptide chains and can be further organised into large oligomeric structures composed of a maximum of six subunits (Hansen and Holmskov 2002). Collectins are soluble pattern recognition receptors (PPRs) specialised at recognising pathogen-associated molecular pattern (PAMPs) of carbohydrate moieties such as lipopolysaccharide (LPS) that are present on microbial surfaces (Janeway 1989; Hansen and Holmskov 1998; Murugaiah et al. 2020). Recognition and binding occur via the CRD regions and can lead to pathogen agglutination, neutralization and/or clearance by opsonization of the microbe and recruitment of phagocytes for clearance (Kishore et al. 2006; Murugaiah et al. 2020). Mice engineered to be genetically deficient in SP-A or SP-D showed increased susceptibility to microbial infections (Levine and Whitsett 2001). Collectins have been found in mammalian species, with CGN, CL-43 and CL-46 predominantly found in Bovidae. It appears that the latter have evolved separately in Bovidae from other mammalian species, but share structural similarities to SP-D, indicating that they may have key roles in health and disease in cattle and related species (Hansen and Holmskov 2002; Gjerstorff et al. 2004a).

The study of bovine collectins and their specific role in bovine infectious disease has been neglected. In comparison, collectin immunobiology is well understood in human and other model systems (e.g., mice) (Murugaiah et al. 2020). In this review, the current knowledge on bovine collectins will be summarised but also gaps in current knowledge will be discussed with respect to findings in human and other mammalian species. It is hoped that this review will be a trigger for new studies on bovine collectins, leading to new approaches for bolstering the immune resilience and defence in cattle.

Genomic Characteristics of Bovine Collectin Family Members

A total of ten collectin genes have been identified in Bovidae, from cattle and other herbivore species. MBL1 and MBL2 encode for MBL-A and MBL-C proteins respectively, SFTPA1 and SFTPD encode for SP-A and D respectively, CGN1 encodes for CGN, CL-43 encodes for collectin 43 (CL-43), CL46 encodes for collectin 46 (CL-46), COLEC10 encodes for liver collectin (CL-L1), COLEC11 encodes for kidney collectin (CL-K1) and COLEC12 encodes for placental collectin (CL-P1) (Hansen and Holmskov 2002; Gjerstorff et al. 2004a; Fraser et al. 2018).

The majority of the bovine collectin genes in *Bos taurus* (SFTPA1, SFTPD, CGN1, MBL1, CL43 and CL46) are located on a single locus on chromosome 28, suggesting evolutionary conservation (Fig. 1). In contrast, the remaining bovine collectin genes are found on separate chromosomes: COLEC11 on chromosome 8, COLEC10 on chromosome 14, COLEC12 on chromosome 24 and MBL2 on

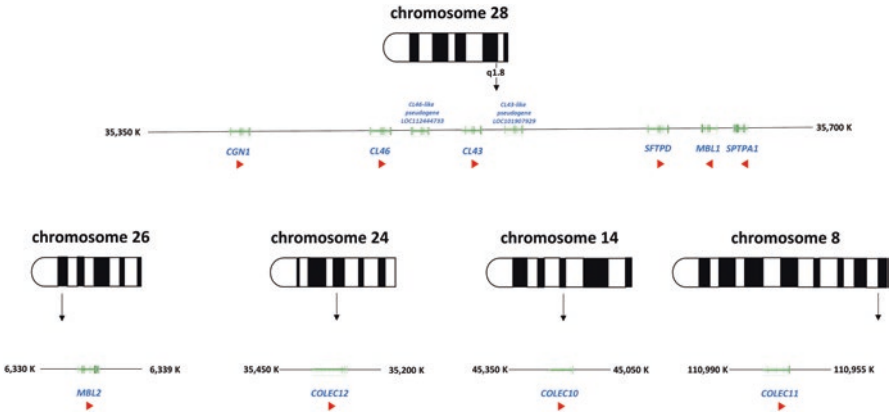

Fig. 1 *Bos taurus* collectin gene loci. Schematic representation of the chromosomal locations of the bovine collectins. The Ensembl accession numbers for each gene are as follows: SFTPA1 (ENSBTAT00000031298); SFTPD (ENSBTAG00000046421); MBL1 (ENSBTAT00000001165); MBL2 (ENSBTAG00000007049); CL43 (ENSBTAG00000047317); CL46 (ENSBTAG00000048082); CGN1 (ENSBTAG00000006536); COLEC10 (ENSBTAG00000017343); COLEC11 (ENSBTAG00000016225) and COLEC12 (ENSBTAG00000007705). (Data taken from Gjerstorff et al. 2004a; Gjerstorff et al. 2004b; and Fraser et al. 2018). Arrows denote direction of transcription

chromosome 26 (Fig. 1). Analysis of the genomic organisation of the collectin genes in *Bos taurus* suggest that they evolved from gene duplication events of a progenitor bovine SP-D gene after *Bovidae* separated into a distinct evolutionary family. Furthermore, CGN has thus only been found in Bovidae species and in addition to cattle (*Bos taurus*), it has also been found in sheep, goat, antelope, bison and several other species (Lu et al. 1993a; Hughes 2007; Mohan et al. 2015; Souza et al. 2018; Barik et al. 2020). Evolutionary analysis of the CRD regions of the additional collectins show that CL-43 and CGN are most similar and probably evolved from a prototype gene that in turn arose from an ancestral SP-D gene for CL-46 and a CGN/CL-43 prototype collectin. In *Bos taurus*, CGN, CL-43 and CL-46 genes are found on distal region of chromosome 28, which is analogous to collectin locus in humans that is located on chromosome 10 (Gallagher et al. 1993; Hansen et al. 2002a, 2003), and comprises the genes encoding MBL (MBL-C), SP-D, SP-A1 and SP-A2 (variants for SP-A) and MBL-A (Sastry et al. 1989; Kolble et al. 1993; Hoover and Floros 1998). Several repetitive and transposon like elements have been observed in CL-43 and CGN genes which may have contributed to gene duplication events at this locus and seems further evolved in the *Bovidae* (Hansen and Holmskov 2002). Other regulatory elements (e.g., promoter regions) of the CL-43 and CGN1 display high sequence similarity to SP-D, suggesting a conservation of the transcriptional control mechanisms governing the expression of these genes (He et al. 2000; Hansen et al. 2002b, 2003).

Diversity, Evolution and Molecular Characteristics of Family Members

The six bovine collectins, whose genes reside on chromosome 28 (SP-A, SP-D, CGN, MBL-A, CL-43 and CL-46), all show interesting structural similarities. Comparing SP-D, CL-43 and CL-46 reveals that they all have an extended collagen-like region of between 35 and 46 nm in length and are longer (by 15 and 25 nm) than the collagen-like region in SP-A and MBL-A. Furthermore, bovine SP-D, CGN and CL-46 has 171 amino acid residues in its collagen-like region, which is 6 fewer amino acids when compared to human SP-D. The bovine collectins also contain two conserved cysteine residues in the N-terminus of the protein, whilst SP-D and CL-43 also have an N-linked glycosylation motif at the start of their collagen-like regions (Lim et al. 1993; Lu et al. 1993b; Crouch et al. 1994; Hansen et al. 2002a; Hansen and Holmskov 2002). Structural studies reveal that the collectins are synthesised as single monomer polypeptides comprising a common CRD, coiled-coil neck, collagenous domain and N-terminal cysteine region (Fig. 2). The collectins then form homotrimeric subunits composed of these three polypeptide chains, except CL-LK which is a heterotrimeric composed of two CL-K1 and 1 CL-L1 polypeptides (Hansen et al. 2016). Most of the collectins can also form higher oligomeric structures with SP-D, CGN, and CL-46 forming cruciforms of four of the subunits, whilst SP-A, MBL-A, MBL-C and CL-LK form tetramer, pentamer or hexamer bouquet structures (Nayak et al. 2012). CL-43 and CL-P1 exit as a monomers, whilst CL-K1 and CL-L1 form dimeric structures (Crouch et al. 1994; Holmskov et al. 1995; Lim and Holmskov 1996; Hansen and Holmskov 1998; Hansen et al. 2016; Paterson et al. 2019) (Fig. 2). CL-P1 also processes a transmembrane domain and an extended α-helical coiled-coil region (Hansen et al. 2016). A comparison of the coding regions of the genes reveals that four exons of similar size encode most of the collagen-like region (Hansen and Holmskov 2002). There are slight differences in size and number of the four exons among the collectins, accounting for some of the structural differences seen. For example, SP-D in human, rat and mouse have collagen regions of 177 amino acid residues in length, compared to bovine SP-D, CGN and CL-46 which have six less amino acid residues (Hansen and Holmskov 2002).

A comparison of the CRDs from the bovine collectins revealed conserved residues among all family members, with CL-43, Cl-46 and CGN clustering together with SP-D confirming their evolutionary ancestry (Fig. 3). CL-P1 was the most divergent of the family, as it has a number of domains (e.g., transmembrane/intracellular domain), showing its unique property of being a membrane bound collectin and possibly a scavenger receptor (Fig. 3) (Ohtani et al. 2001). A comparison of the CRD from CGN from several species of Bovidae revealed a hide degree of conservation in the domain, suggesting the importance of this collectin to ruminant immunobiology (Fig. 4). The CRD of *B. taurus* CGN clustered together with that from *B. bison* and *B. indicus* × *B.* taurus and are closely related (Fig. 4). It would be interesting to further investigate the properties of these closely related CGNs

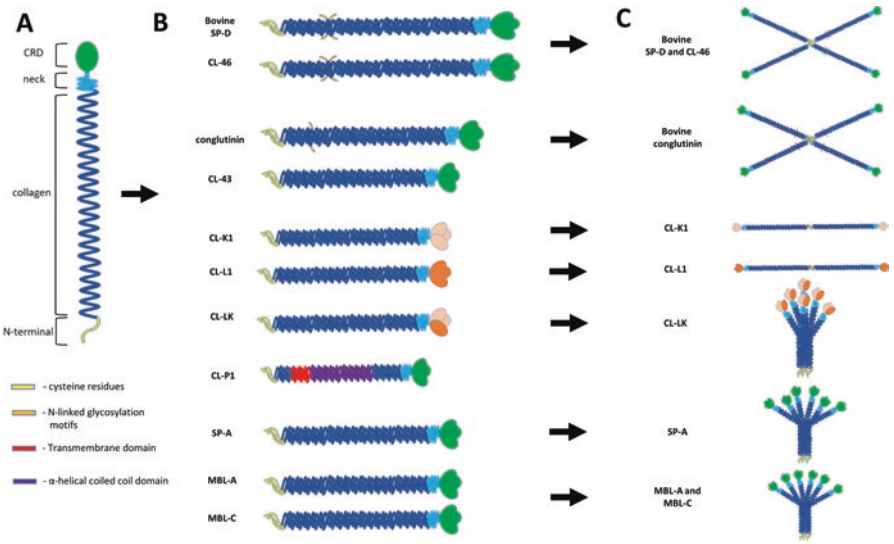

Fig. 2 Molecular structural characteristics of the bovine collectins. (**A**) Domain organization of collectin polypeptide monomer chain showing the carbohydrate recognition domain (CRD), coiled neck region, collagen domain and N-terminal domain. Each collectin has variations on this basic structure such as length and modifications. (**B**) Trimers of the bovine collectins are each built up by the association of three monomer polypeptide chains with the collagen regions intertwining to form a collagen triple helix. Individual collectins vary in length and modification (e.g., glycosylation). All the bovine collectins are soluble, except for CL-P1 which has a transmembrane/intracellular domain at its N-terminus and an α-helical coiled-coil domain. CL-LK is the only collectin to form a heterotrimer comprising of 2 CL-K1 and 1 CL-L1 monomers. (**C**) Collectins can form higher oligomeric structures. SP-D, CL-46 and conglutinin can form dodecamer cruciforms, comprising of four trimers. CL-K1 and CL-L1 are can form dimeric forms. MBL-A, MBL-C, SP-A and CL-LK can all from pentameric of hexameric bouquet-type structures

experimentally, since apart from cattle, the other Bovidae's CRDs that have been studied come from wild animals that have a diverse life-cycle and are not under managed breeding. Therefore, their innate immune markers, e.g., CGN may have undergone a natural selection process, altering the molecule's property, perhaps making it more effective. From the data, it appears that any changes to the CGN CRD from wild Bovidae are small and subtle, but this may enhance and widen the carbohydrate binding properties of CGN (Fig. 4).

Genetic Variation and Associations with Disease Susceptibility

Several insertion/deletion (InDels), single nucleotide polymorphisms (SNPs) and other genetic variations in the collectin genes are associated with susceptibility to infectious diseases in a number of species. However, in the bovine collectin genes, the nature and consequence of mutations has yet to be been explored fully, with only

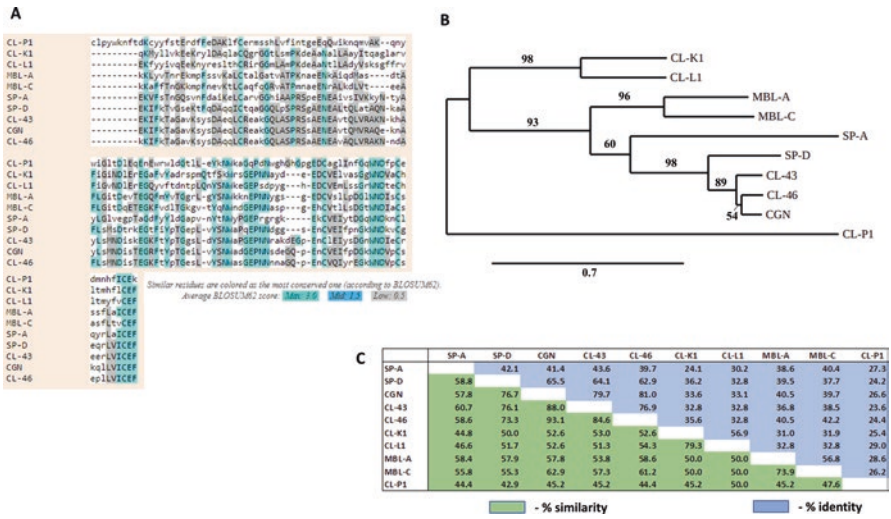

Fig. 3 Diversity and evolution of the CRD of the bovine collectins. (**A**) Protein sequences for the carbohydrate recognition domain (CRD) of each bovine collectin was selected (using the NCBI annotation positions) from amino acid motif EKIF to the CEF motif at the C-terminus. Sequences were aligned on the phylogeny.fr site (www.phylogeny.fr) using MUSCLE, with GBlocks curation. Conserved residues are shown in capitals and colours. (**B**) Phylogenetic tree of the CRD of the bovine collectins was done on the phylogeny.fr site and was based on the BioNJ algorthim with the Jones-Taylor-Thornton matrix with a gamma-distribution parameter of $a = 2.09$ (based on 118 amino acid sites). Numbers on the branches are percentages of 1000 bootstrap samples supporting a given branch. (Jones et al. 1992; Edgar 2004; Dereeper et al. 2008; Fraser et al. 2018). (**C**) Percentage similarity and identity matrices for bovine collectin CRDs were compiled using MatGAT (Campanella et al. 2003). Protein accession numbers are as follows: SP-A (NP_001071306.2), SP-D (NP_851369.1); CGN (NP_783630.2); CL-43 (NP_001002237.1); CL-46 (NP_001001856.1); CL-K1 (NP_001069771.1); CL-L1 (NP_001192642.1); CL-P1 (NP_001095313.1); MBL-A (NP_001010994.1) and MBL-C (NP_776532.1)

a few studies mainly describing genetic variability in bovine MBL genes. Mutations in the bovine MBL genes are associated with mastitis and milk production (Wang et al. 2011, 2012). Three SNPs were identified in the MBL1 from Chinese native cattle that were linked to mastitis resistance and increased milk production (Wang et al. 2011). Another study identified four SNPs in exon 1 of MBL2 in Chinese Holstein cattle and Luxi yellow cattle linked to mastitis and altered complement activity (Wang et al. 2012). Mastitis is commonly measured from the somatic cell score (SCS), which analyses the inflammatory cell content of milk. Other studies have also found mutations in the MBL1 and MBL2 genes of cattle and their links to SCS and complement activity (Liu et al. 2011; Zhao et al. 2012; Yuan et al. 2013). In other animals, mutations in the porcine MBL2 gene are linked with lower levels of MBL-C and are associated with pulmonary, gastro-intestinal infections and septicaemia (Lillie et al. 2007), whilst a SNP in porcine MBL1 is linked with lower levels of MBL-A (Juul-Madsen et al. 2011). Interestingly, polymorphisms at the MBL2 locus of water buffalo (*Bubalus bubalis*) have been reported to correlate with

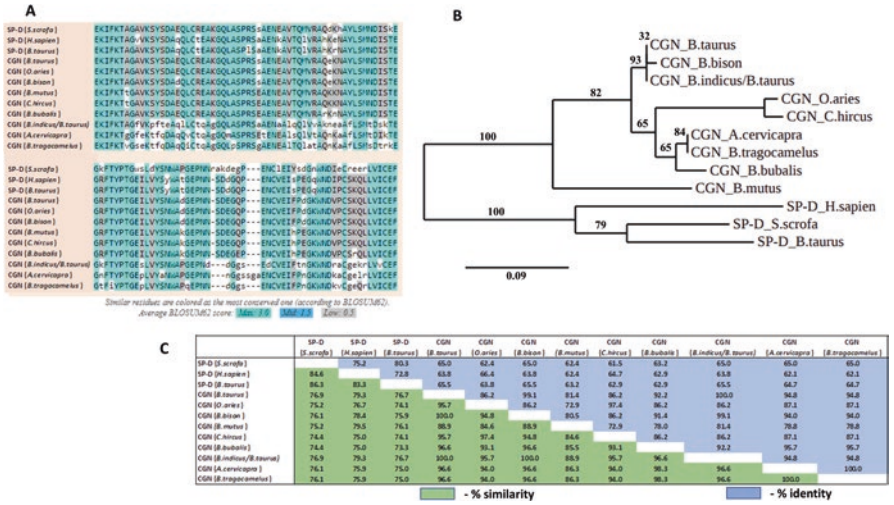

Fig. 4 Diversity and evolution of the CRD of conglutinin from different Bovidae species. (**a**) Protein sequences for the carbohydrate recognition domain (CRD) of each conglutinin collectin was selected (using the NCBI annotation positions) from amino acid motif EKIF to the CEF motif at the C-terminus. Sequences were aligned on the phylogeny.fr site (www.phylogeny.fr) using MUSCLE, with GBlocks curation. Conserved residues are shown in capitals and colours. (**b**) Phylogenetic tree of the CRD of the bovine collectins was done on the phylogeny.fr site and was based on the BioNJ algorthim with the Jones-Taylor-Thornton matrix with a gamma-distribution parameter of $a = 2.09$ (based on 118 amino acid sites). Numbers on the branches are percentages of 1000 bootstrap samples supporting a given branch (Jones et al. 1992; Edgar 2004; Dereeper et al. 2008; Fraser et al. 2018). (**c**) Percentage similarity and identity matrices for conglutinin CRDs were compiled using MatGAT (Campanella et al. 2003). Protein accession numbers are as follows: SP-D (S. scrofa) (NP_999275.1); SP-D (H. sapien) (NP_003010.4); SP-D (B. taurus) (NP_851369.1); CGN (B. taurus) (NP_783630.2); CGN (O. aries) (AFH75399.1); CGN (B. bison bison) (XP_010832460.1); CGN (B. mutus) (ELR45583.1); CGN (C. hircus) (XP_005699317.2); CGN (B. bubalis) (XP_006064838.1); CGN (B. indicus × B. taurus) (XP_027386536.1); CGN (A. cervicapra) (AGK36277.1); CGN (B. tragocamelus) (ADU25247.1)

resistance to *Brucella abortus* infection and susceptibility (Capparelli et al. 2008). In the porcine host, three SNPs within gene MBL1 were also found to correlate with disease susceptibility (Lillie et al. 2006b). Furthermore, in humans, MBL2 SNPs have been also been observed to increase susceptibility to several bacterial, viral, and parasitic infections, as well as ischemia–reperfusion injury, hepatitis, cystic fibrosis and autoimmune conditions such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) (Eisen and Minchinton 2003; Holmskov et al. 2003; Takahashi et al. 2005). In cattle, polymorphisms in the bovine MBL or other collectin genes and susceptibility to bovine tuberculosis is unknown, but studies in human tuberculosis are intriguing. Normal or increased levels of MBL seem to be associated with common infection with *Mycobacterium tuberculosis* and *Mycobacterium leprae* (Garred et al. 1994, 1997), whilst approximately 30% of healthy persons have mutations associated to MBL deficiency and are associated

with susceptibility to tuberculosis and other inflammatory conditions in some ethnicities (Takahashi and Ezekowitz 2005; Thiel et al. 2006; Goyal et al. 2016).

Further insight into the consequences of genetic variability in the bovine collectins was provided in a recent study utilising next-generation sequencing (NGS) to analyse genetic variations in bovine collectins and ficolins from 120 cattle, 80 of which had infection and 40 that were apparently healthy (Fraser et al. 2018). This study found short nucleotide variants (SNVs) in the bovine collectin genes, with 74 variants that were associated with infectious disease (Fraser et al. 2018). Most of these genetic variants seem to be clustered in a 29-KB region upstream of the collectin locus on bovine chromosome 28 (Fraser et al. 2018). Using computational analysis, this study also predicted SNVs in the exons, introns, putative transcription binding factor sites that were likely to alter expression, structure and function of some collectin proteins, revealing potential susceptibility markers for bovine infections (Fraser et al. 2018). Potential deleterious mutations resulting in the following amino acid changes were identified in collagen-like domains of MBL2 (Pro42Gln), SFTPD (Pro132Ser), CGN (Arg173His), CL46 (Pro185Leu) and in CL43 (Thr117Ala and Gln185His), and in the CRDs of CGN (Glu302Asp) and SFTPD (Ala288Gly) (Fraser et al. 2018). The significance of these mutations has yet to be determined experimentally, but all these collectins have been associated with infectious disease susceptibility. For example, low plasma level of CGN has been implicated in increased risk of respiratory infection in cattle (Holmskov et al. 1998), whilst elevated level of CL-46 in calves has been found to be associated with resistance to parasitic infection (Li et al. 2011) as well as the associations of MBL mutations with mastitis (mentioned above). The concentration of genetic variation upstream of the collectin locus on chromosome 28 could also be indicative of important regulatory elements that control the expression of these collectins (Fraser et al. 2018). The above findings show the potential of expanding these genome-wide association studies on the bovine collectin genes to gain further insights into the genetic susceptibility to the major infectious diseases (e.g., bovine tuberculosis, RBS and mastitis) among different cattle breads.

Tissue Distribution, Physiological Role, and Protection Against Antimicrobial Infection

The ability of collectins to distinguish between self and non-self is dependent on the types of sugar moieties on glycoconjugates on the cell surface. These are essentially either monosaccharide or disaccharide in nature. Collectin CRDs generally favour binding of mannose-like ligands or L-fucose (Iobst and Drickamer 1994). SP-D prefers maltose, whilst CGN and CL-46 prefer N-acetylglucosamine and CL-43 prefers D-mannose (Lu et al. 1992; Holmskov et al. 1993; Hansen et al. 2002a; Paterson et al. 2019). These sugars are commonly found on microbial surfaces but are rare in self-glycoproteins (Drickamer and Taylor 1998). Moreover, microbial

targeting and clearance is facilitated by some collectins (e.g., SP-D, CGN, CL-46) higher order multimeric forms (e.g., cruciform) which mediate bridging interactions between different ligands, as opposed to trimeric subunit forms (e.g., SP-A, MBL and CL-43) (Hartshorn et al. 1993a). An overview of the literature to date is presented below on the bovine collectins and their roles in health and disease in the *Bovidae* or extrapolated from studies in other mammalian systems.

Surfactant Protein A and D

The composition of pulmonary surfactant consists of 90% phospholipid and 10% protein. This protein proportion contains four types of surfactant proteins (SP-A, SP-B, SP-C and SP-D). SP-B and SP-C are hydrophobic in nature and crucial for the physiological maintenance of the alveolar membrane surfaces. Conversely, SP-A and SP-D are hydrophilic proteins and have an important role in immunity in the lung. In mammals, SP-A and SP-D have been studies most extensively in human and mouse, but there are limited studies on the specific role they play in the Bovidae. We will review the general properties of SP-A and SP-D and what is currently known about their specific role in the Bovidae.

SP-A is mainly found in the alveoli and is synthesised by type II alveolar cells and the non-ciliated bronchial epithelial Clara cells (Voorhout et al. 1992; Nayak et al. 2012). Unlike SP-D, extrapulmonary expression of SP-A is limited to only a few tissues including in the human and rat small intestine the murine uterus, fetal membranes, human prostate, amniotic fluid, thymus and salivary gland (Van Iwaarden et al. 1990; Miyamura et al. 1994; Lin et al. 2001; Madsen et al. 2003) (Table 1). In bronchoalveolar lavage fluid (BALF) obtained from Holstein steers calves, the approximate SP-A concentration was 35 ng/mL whereas the serum concentration was 7.8 ng/mL (Eberhart et al. 2017).

SP-D is also predominately found in the pulmonary alveoli surfaces and is also synthesised by type II alveolar cells, non-ciliated bronchial epithelial Clara cells and serous cells of the trachea-bronchial glands (Crouch et al. 1992; Voorhout et al. 1992; Wong et al. 1996; Nayak et al. 2012). Unlike SP-A, SP-D is synthesised in a wide variety of tissues in mammals, including the trachea, placenta, prostate, small intestine brain, heart, kidneys, testis, salivary gland, and pancreas (Murugaiah et al. 2020) (Table 1). Low level of SP-D has also been detected in spleen, uterus, adrenal and mammary tissues (Fisher and Mason 1995; Madsen et al. 2000; Hogenkamp et al. 2007). SP-D is also present in the epithelial cells of various tissues (parotid, lacrimal and sweat glands, intra-hepatic bile ducts, gall bladder, esophagus, pancreas, urinary tract and fetal membranes (Miyamura et al. 1994; Madsen et al. 2000; Brauer et al. 2007). SP-D has been detected in alveolar macrophages, but is not synthesised in these cells, but rather internalize into the phagolysosomal compartment, where it is broken down (Dong and Wright 1998). Similar to the above mammalian studies, the expression of bovine SP-D has been observed in the lungs, mammary glands and gastrointestinal tract (Gjerstorff et al. 2004b). In humans, the

Table 1 Origin of bovine collecting and their tissue distribution

Collectin	Tissue of origin	Tissue of presentation	Comments
SP-A	Type II alveolar cells and the non-ciliated bronchial epithelial Clara cells	Alveolar space, mucosal surfaces, thymus? Uterus? prostate?	SP-A is limited to the lungs (alveoli), but there may be extrapulmonary expression of SP-A in other tissues in Bovidae which has been noted in other mammals. Role in antimicrobial innate immunity including opsonization, neutralization and clearance
		Amniotic fluid? salivary gland?	
SP-D	Type II alveolar cells, non-ciliated bronchial epithelial Clara cells and serous cells of the trachea, intestinal mucosa? thymus? prostate? mammary gland	Alveolar space, mucosal surfaces, semen, udder, trachea? placenta? prostate? small intestine? Serum?	SP-D expression has been detected in many non-pulmonary tissues in mammals and has been observed in the bovine lung and udder suggestion an important role in protection from mastitis
MBL	Liver and small intestine (rumen?) udder?	Serum	Bovidae have two different MBL proteins (A and C). Key antimicrobial collectin and has a broad role in innate immunity including opsonization, neutralization and complement activation
Conglutinin, CL-43 and CL-46	Liver	Serum	Unique to Bovidae and may have a role in antimicrobial defence and controlling general inflammatory response, e.g., in pneumonia, gastroenteritis and mastitis
CL-P1	Unknown in Bovidae. Placenta? Endothelial cells	Endothelial cells?	CL-P1 is the only membrane bound collectin, with some unique structural aspects. Role unknown in Bovidae but may be involved in complement activation
CL-K1	Unknown in Bovidae	Serum	Role unknown in Bovidae, but forms dimers and a heterotrimeric complex with CL-L1. Phylogenetically closely related to CL-L1
CL-L1	Unknown in Bovidae. Liver?	Unknown but ubiquitous in other mammals	Role unknown in Bovidae, but forms dimers and a heterotrimeric complex with CL-K1. Phylogenetically closely related to CL-K1. Possibly expressed in bovine liver and may be involved in embryonic development

concentration of SP-D in BALF ranges between 0.1 and 0.9 mg/mL and makes up about 0.5% of the protein content in the alveoli (Hartshorn et al. 1994; Honda et al. 1995). The serum concentration in healthy humans is approximately 66 ng/mL (Honda et al. 1995). In healthy calves, the mean BALF and serum concentration was determined to be 22 ng/mL and 9 ng/mL, respectively (Eberhart et al. 2017). The levels of SP-D in the bovine host seems to be significantly lower than in humans. It is not clear why this is the case but could be an indication of a greater role being played by other bovine collectins in the lungs (e.g., CGN).

Both SP-A and SP-D are well known to have anti-microbial properties and are significantly elevated in the mammalian infected lung and in response to allergens and hypoxia (Atochina et al. 2001; White et al. 2001; Kasper et al. 2002). The lung and serum concentrations of SP-A has not been shown to fluctuate significantly upon infection, particularly in bovine respiratory disease (BRD) (Eberhart et al. 2017). However, gross examination of cattle infected with tuberculosis showed increased immunostaining for SP-A in the type II pneumocytes surrounding the granulomas observed in the tissue (Beytut 2011). Similar findings were also reported for SP-A in the human lung infected with tuberculosis (Stanton et al. 2003). Both SP-A and SP-D bind to several microbes including viruses, bacteria, fungi and parasites and has been comprehensively reviewed recently (Murugaiah et al. 2020). SP-A and SP-D facilitate clearance of microbes by direct lysis, agglutination or neutralization and/or subsequent opsonization by phagocytes (Holmskov et al. 2003; Wu et al. 2003). SP-D gene knockout mice (SP-D$^{-/-}$) have elevated pulmonary macrophages and enhancement pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), inhibition of lymphocyte proliferation and reactive oxygen species (ROS) in the alveoli, suggesting that SP-D has an anti-inflammatory effect in lung immunity and infection (Botas et al. 1998; Korfhagen et al. 1998; Ikegami et al. 2000; Borron et al. 2002). SP-D is, therefore, likely to play a key role in regulating the local immune response in tissues that are particularly exposed to microbes by balancing the processes for microbial clearance with that of organisms, by a combination of enhancing the microbial elimination and reducing inflammation. This type of immune regulation is particularly key in the bovine udder, where control of mastitis is critical for the optimum stimulation of milk secretion pathways and high yielding milk production in dairy cattle. Bovine SP-D is expressed in the udder and has a higher expression than in the bovine lung, when compared to the of SP-D expression of human mammary tissue versus lung tissue (Madsen et al. 2000; Gjerstorff et al. 2004b). This suggests an important role for bovine SP-D in controlling infection in the udder. It is also intriguing that polymorphisms in the bovine SP-D gene have been found which may be linked with disease susceptibility (e.g., mastitis) (Gjerstorff et al. 2004b). Furthermore, in the bovine gastrointestinal system, regulation of the immune response against pathogens is also of key importance as ruminants need the symbiotic relationship with microbes for normal health. It is therefore likely that the bovine collectins (e.g., SP-D and CGN) play a key role in modulating the immune response against microbes in these tissues.

Numerous studies on the interaction of SP-A and SP-D with microbes have been reported in human and other mammals, but there are little specific studies in the

Bovidae (Murugaiah et al. 2020). However, studies on Gram-positive and Gram-negative bacteria, mycobacteria, and common respiratory viruses can be extrapolated to the Bovidae, where similar molecular mechanisms and outcomes may be seen.

SP-A and SP-D both bind to many Gram-negative and Gram-positive bacteria, particularly known respiratory pathogens, e.g., *Klebsiella pneumoniae, Pseudomonas aeruginosa*, mycobacteria, *Mycoplasma pneumoniae, Haemophilus influenzae, Legionella pneumophila* and *Streptococcus pneumoniae*, among others (Murugaiah et al. 2020). Several consequences from these interactions have been observed, including aggregation, enhanced uptake and clearance by phagocytes and even direct effects on bacterial growth (Pikaar et al. 1995; Murugaiah et al. 2020). SP-A and SP-D bind to different sites on the LPS ligand in Gram negative bacteria (SP-A: lipid A; SP-D: O-antigen and terminal oligosaccharides) (Kuan et al. 1992; Van Iwaarden et al. 1994). Furthermore, SP-A is also able to bind to capsular polysaccharides of *Klebsiella*, outer membrane protein (OMP) of *H. influenzae*, but does not bind to peptidoglycan (Mcneely and Coonrod 1994; Kabha et al. 1997; Murakami et al. 2002). SP-A also aggregates and enhances phagocytosis of *H. influenzae* and *K. pneumoniae* by macrophages (Mcneely and Coonrod 1994; Kabha et al. 1997). SP-D also binds to cell membrane lipids of *M. pneumoniae* (Chiba et al. 2002). SP-A and SP-D can also inhibit the growth of *M. pneumoniae*, *Escherichia coli*, *K. pneumoniae*, *Enterobacter aerogenes* and *P. aeruginosa* by compromising bacterial membrane integrity, increasing permeability or inhibiting metabolic pathways (Van Iwaarden et al. 1994; Wu et al. 2003; Piboonpocanun et al. 2005).

Of particular interest is respiratory infections with mycobacteria, where bovine tuberculosis continues to be a severe cause of morbidity and mortality of cattle in the UK and worldwide (Miles 2009; Abernethy et al. 2013; APHA 2020). The interaction of mycobacteria with bovine SP-A and SP-D has not been characterised, but there are numerous studies investigating these surfactant proteins in human and rodents infected with *M. tuberculosis* and *M. bovis* BCG bacilli. SP-A can binds to *M. tuberculosis* Apa glycoprotein on its surface (Ragas et al. 2007), whilst SP-D binds to Gram-positive ligands lipoteichoic acid, peptidoglycan and mycobacterial lipoarabinomannan (LAM) (Ferguson et al. 1999; Van De Wetering et al. 2001; Kudo et al. 2004). Both SP-A and SP-D can bind and agglutinate *M. tuberculosis*, but interestingly, they have opposing downstream effects by macrophages. SP-A enhances phagocytosis by macrophages mediated by upregulation of expression of the mycobacterial receptor, mannose receptor on the macrophage (Beharka et al. 2002). In fact, both SP-A and SP-D can facilitate phagocytosis without the need for direct microbial binding, by enhancing the expression of such cell surface phagocytic receptors on the macrophage (Beharka et al. 2002; Kudo et al. 2004). In contrast, SP-D inhibits phagocytosis by macrophages by blocking the interaction of LAM with mannose receptor (Ferguson et al. 1999, 2002). Binding of CGN to *M. bovis* BCG also results in inhibition of phagocytosis by macrophages, and thus, a similar mechanism has been proposed (Mehmood et al. 2019). However, SP-A$^{-/-}$, SP-D$^{-/-}$, and SP-A/D$^{-/-}$ knockout mice infected with *M. tuberculosis* could still

clear infection, questioning the relevance of the rodent model to human and bovine tuberculosis (Lemos et al. 2011).

Both SP-A and SP-D can also modulate the downstream adaptive response against pathogens. SP-A inhibits TNF-α secretion, via a toll-like receptor 2/NF-κB mediated mechanism (Murakami et al. 2002). SP-A and SP-D can also modulate the phagolysosome by promoting reactive oxygen and nitrogen intermediates enhancing intracellular killing, particularly in the case mycobacterial infection. SP-A enhances the killing of intracellular *M. bovis* BCG by increasing nitric oxide (NO) production and enhancing the pro-inflammatory cytokines, e.g., TNF-α (Weikert et al. 2000). But curiously, in alveolar macrophages primed with IFN-γ and infected by mycobacteria, SP-A decreased intracellular NO by inhibiting TNF-α secretion and nuclear factor-kappa B (NF-κB) activation (Pasula et al. 1999; Hussain et al. 2003). SP-A and SP-D can also directly bind to cell surface PRRs, such as Toll-like receptors (TLRs) and CD14, influencing the inflammatory response (Borron et al. 2000; Sano et al. 2000; Murakami et al. 2002). In tuberculosis, SP-A has been shown to promote both inflammation in the presence of infection and suppresses inflammation in uninfected macrophages, and thus probably controlling the inflammatory response against host-mediated tissue damage in the lung (Gold et al. 2004).

SP-A and SP-D can also bind and influence the outcome of viral infection enhancing viral phagocytosis and neutralisation (Murugaiah et al. 2020). Bovine SP-D is able to bind to bovine rotaviruses (Nebraska calf diarrhoea virus strain), targeting the VP7 glycoprotein (Reading et al. 1998). Bovine SP-D was also able to inhibit hemagglutination of rotavirus and neutralise infectivity; neutralization of rotavirus by bovine SP-D was dependent on the glycosylation of VP7 (Reading et al. 1998). Studies in animal models has also shown the importance of collectins in protection against viral infection. In studies with SP-A$^{-/-}$ and SP-D$^{-/-}$ knockout mice that were infected with Influenza A virus (IAV), both collectins are protective, but this is also dependent on the glycosylation of hemagglutinin (HA) and neuraminidase (NA) antigens (Levine and Whitsett 2001; Levine et al. 2002; Hawgood et al. 2004). Furthermore, in mice, it seems SP-D plays a greater role in IAV protection as it enhances the clearance of infection, whereas SP-A does not (Levine et al. 2001; Hawgood et al. 2004). SP-A binds to IAV mannose residues on HA and NA resulting in viral neutralisation and inhibition of release of viral particles from infected cells (Malhotra et al. 1994; Benne et al. 1995). SP-D also strongly inhibits IAV hemagglutination and promotes viral aggregation and neutralisation (Hartshorn et al. 1994). SP-A and SP-D also inhibit NA enzymatic activity, but this is much stronger with SP-D, but these interactions also seem to be dependent on the viral strain (Reading et al. 1997; Tecle et al. 2007; Job et al. 2010). Recombinant truncated forms of SP-A (rfhSP-A) and SP-D (rfhSP-D), composed of the α-helical neck and CRD domains have also been studied in IAV infection. rfhSP-A promotes IAV infection, replication and enhancement of the pro-inflammatory response, whereas full-length SP-A inhibits IAV infection and dampens the pro-inflammatory response, demonstrating that the full-length SP-A molecule is required for IAV protection (Al-Qahtani et al. 2019). In a similar study, rfhSP-D-was able to inhibit IAV entry, down-regulate key viral factors (M1) and dampen the pro-inflammatory

response (Al-Ahdal et al. 2018). These studies using rfhSP-A and rfhSP-D have provided greater understanding of the IAV infection process and the possible application of rfhSP-D in anti-viral therapy. SP-D also enhances IAV uptake by neutrophils and virus-induced respiratory burst, but SP-A (and mucins and gp-340) inhibit this effect, reducing the ability of SP-D to facilitate neutrophil viral clearance (White et al. 2001). SP-A is also able to bind to herpes viruses (Herpes Simplex virus type 1 (HSV-1), Cytomegalovirus), enhancing phagocytosis of the virus by macrophages (Van Iwaarden et al. 1991, 1992; Weyer et al. 2000). SP-D activity against herpesviruses has not been reported. SP-A and SP-D are also able to bind to Respiratory Syncytial virus (RSV) and are important for neutralising infectivity and enhancing viral clearance (Ghildyal et al. 1999; Hickling et al. 1999; Levine et al. 1999; Sano et al. 1999, 2000). SP-D is able to bind to glycosyl moieties on viral spike protein (S-protein) of the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV). Increased serum levels of SP-D have also been reported in SARS patients (Leth-Larsen et al. 2007; Wu et al. 2009). Furthermore, both SP-A and SP-D bind to other coronavirus strains (HCoV-229E) and inhibit viral infection of human bronchial epithelial (16HBE) (Funk et al. 2012). It is unknown whether these collectins have any effect on novel coronavirus SARS-CoV-2, which is responsible for the COVID-19 pandemic, but the above data seems to suggest that SP-A and SP-D may play a protective role. In another recent emerging viral disease, SP-D has been shown to bind Ebola virus glycoprotein and enhance viral infection, suggesting a role in pathogenesis (Favier et al. 2018). In mice, SP-D has been observed to have a protective role against Vaccinia virus infection (Perino et al. 2013). SP-A has also been reported to enhance clearance of adenovirus infection in the lungs while dampening the immune response (Harrod et al. 1999).

Several studies have reported interesting interactions of SP-A and SP-D with Human Immunodeficiency virus-1 (HIV-1). SP-A and SP-D bind to the HIV-1 gp120 viral glycoprotein and inhibit direct viral infection of $CD4^+$ T cells (Meschi et al. 2005; Gaiha et al. 2008), but in dendritic cells (DCs), SP-A has the opposite effect, increasing HIV infectivity, and thus facilitating transfer of the virus from DC to $CD4^+$ T cells (Gaiha et al. 2008). The truncated rfhSP-D is also able to bind to HIV-1 gp120 and prevent infection of Jurkat T cells, U937 monocytic cells and PBMCs, but importantly also suppresses the viral-induced cytokine response from these cells (Pandit et al. 2014). In a follow-up study, rfhSP-D was also found to bind to dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) receptor, modulating the binding of HIV-1 and its transfer to $CD4^+$ T cells (Dodagatta-Marri et al. 2017). rfhSP-D has also been reported to block infection of HIV-1 across the vaginal epithelium (Pandit et al. 2014). As reported above with studies in IAV, rfhSP-D has a potential prophylactic and therapeutic potential against HIV-1 infection.

There have also been several studies showing the anti-fungal activity of SP-A and SP-D (Murugaiah et al. 2020). To date, the bovine SP-A and SP-D have not been shown to interact with fungal pathogens that infect the Bovidae. There is considerable scope here for further investigation as several fungal species (e.g., Candida and Aspergillus) are responsible for mastitis, abortion, otitis externa,

gastrointestinal infections, and pneumonia (Seyedmousavi et al. 2018). In particular, a common fungal disease in cattle is Ringworm caused by *Trichophyton verrucosum*, but no studies have been conducted on its possible interaction with collectins. An overview of SP-A and SP-D antifungal activity in other mammals will be presented and extrapolated to Bovidae where appropriate.

Both SP-A and SP-D can bind to the conidia of *Aspergillus fumigatus* and inhibit conidia infectivity and promote enhancement of phagocytosis and intracellular killing by neutrophils and alveolar macrophages (Madan et al. 1997). SP-A and SP-D can also inhibit the growth of *Histoplasma capsulatum*, but no effect is seen on aggregation or phagocytosis (Mccormack et al. 2003). SP-A has also been reported to bind to *Cryptococcus neoformans* (both encapsulated and non- encapsulated yeast form), but no enhancement of phagocytosis of the acapsular form was observed either (Walenkamp et al. 1999). SP-A and SP-D can also bind to *Coccidioides posadasii* and the fungus is also able to inhibit the expression of SP-A and SP-D in the lungs, possibly facilitating pathogenesis (Awasthi et al. 2004). SP-D can bind to *Candida albicans*, agglutinating the fungus and directly inhibiting its growth (Van Rozendaal et al. 2000; Awasthi et al. 2004), whilst SP-A is also able to bind to *C. albicans* and interfere with its attachment to alveolar macrophages, inhibiting phagocytosis and the pro-inflammatory response (Rosseau et al. 1997). This may be relevant in Bovidae, as candidiasis is reported in several conditions in ruminants (Seyedmousavi et al. 2018). SP-D also binds to *Saccharomyces cerevisiae* (Allen et al. 2001a, b). The opportunistic fungus Pneumocystis can infect several mammals in a species-specific manner and has been reported in calves and sheep (Settnes and Henriksen 1989). The interaction of bovine SP-A and SP-D with *Pneumocystis* in the Bovidae has not been reported, but studies in other mammalian species suggests they may play an important role in this opportunistic infection. Both SP-A and SP-D are able to bind to *Pneumocystis* via its major surface glycoprotein, resulting in aggregation and attachment to the alveolar epithelium in Pneumocystis pneumonia, but this does not increase its phagocytosis (Zimmerman et al. 1992; O'Riordan et al. 1995; Mccormack et al. 1997a, b; Vuk-Pavlovic et al. 2001). SP-D mediated aggregation of *Pneumocystis* may inhibit phagocytosis by macrophages and facilitate persistence of the fungus within the lung (Vuk-Pavlovic et al. 2001). In pneumocystis pneumonia, there is also an increase in the expression of SP-A and SP-D in the lungs (Phelps et al. 1996; Aliouat et al. 1998; Atochina et al. 2001; Qu et al. 2001). SP-A enhances attachment of *Pneumocystis* to rat alveolar macrophages *in vitro* (Williams et al. 1996) but reduces phagocytosis of the fungus in human alveolar macrophages *in vitro* (Koziel et al. 1998). Thus, enhanced levels of SP-A in *Pneumocystis* pneumonia may facilitate pathogenesis, whilst SP-D may contribute to fungal clearance.

Parasitic infections are also fairly common in cattle and other Bovidae species. This can have implications on general health, reproduction, growth, productivity of meat and milk and may result in death in severe infections. Parasitic diseases of cattle are commonly caused by protozoa, helminths (roundworms, tapeworms and flukes). To date, very little has been reported on the interaction of bovine collectins and parasitic infections of cattle. Some of these diseases are also important zoonotic

infections (Mcdaniel et al. 2014), so further studies are needed to determine whether collectins may play a role in bovine parasitic infection and transmission to humans. In general, there are also a limited number of functional studies on the role of SP-A and SP-D in protozoal and helminth infections in other mammalian species. In mice, it has been reported that there are increased serum levels of SP-D in renal and cerebral tissues, in animals experimentally infected with *Plasmodium berghei*, compared to controls (Cahayani et al. 2016). SP-D has also been reported to bind to the surface of *Schistosoma mansoni* larval stages, but it remains unknown what effect this has on the parasite (Van De Wetering et al. 2004a, b). However, SP-D may be essential for protection against helminth infection, since a study using an experimental model system showed that *Nippostrongylus brasiliensis*-infection of SP-D$^{-/-}$ knockout mice caused severe susceptibility to parasitic disease, whilst treatment with rfhSP-D enhanced parasite clearance and anti-parasitic immune responses (Thawer et al. 2016). SP-D was also able to directly bind to *N. brasiliensis* larvae and enhance its killing by alveolar macrophages (Thawer et al. 2016).

In ruminants, serum collectins such as SP-D and CGN may likely play a role in gastrointestinal and systemic infections from parasites. However, specific data on the involvement of collectins and parasitic infections is lacking, but gauging from studies in other mammals, much could be learned.

Mannan-Binding Lectin

Bovidae, as in most mammals, have two MBL genes (MBL1 and MBL2), which encode the MBL-A and MBL-C proteins, respectively (Loveless et al. 1989; Gjerstorff et al. 2004a). In mammals, MBL-A and MBL-C are serum proteins that are mainly synthesised by the liver and small intestine (Ezekowitz et al. 1988; Sastry et al. 1991; Hansen et al. 2000) (Table 1). In mice, mRNA expression of MBL genes was also detected in various other tissues (Shushimita et al. 2015), and this may also be these case for Bovidae, particularly the rumen and udder. The normal serum concentrations of bovine MBL-A and MBL-B have not been clearly defined but are estimated to be 0.8–7.4 μg/mL (Wang et al. 2012). MBL is a key anti-microbial collectin and has a broad role in innate immunity including opsonization, neutralization and complement activation (Van De Wetering et al. 2004a). The CRD of MBL selectively targets microbes by binding to cell-surface to mannose and N-acetylglucosamine residues and subsequent activation of MBL-associated serine proteases (MASPs) 1 and 2, leading to complement activation via the Lectin pathway, inducing phagocytic and inflammatory responses (Thiel et al. 1997; Matsushita et al. 2001; Sorensen et al. 2005).

Mastitis is a major disease of dairy cattle and is characterised by inflammation of the mammary gland brought on by infection of the udder. This decreases the quality and quantity of milk production, reduction in lactation, and in severe cases, early culling, resulting in a significant economic burden (Miller et al. 1993; Seegers et al. 2003). The main pathogens involved in mastitis are bacteria such as *E. coli*,

Staphylococcus aureus, *Streptococcus dysgalactiae*, *Streptococcus uberis* and *Streptococcus agalactiaeare*, although some fungi may also rarely be involved. Host resistance to mastitis is a known trend and there has been a concerted effort to identify immune response genes that may play a role in this and will be favourable traits for selective breeding (Oviedo-Boyso et al. 2007; Swanson et al. 2009). The MBL genes have been implicated as playing a probable role in mastitis susceptibility in cattle. Furthermore, In pigs and mice, MBL-A is able to bind target bacteria (Lillie et al. 2006a, b; Phaneuf et al. 2007). Mutations in both MBL1 and MBL2 genes are also suggestive of susceptibility of animals to infection (Shi et al. 2004; Lillie et al. 2005, 2007; Capparelli et al. 2008), leading to lower serum levels of MBL and likely compromising innate immune responses (Madsen et al. 1995; Capparelli et al. 2008).

There is little data on the specific activity of bovine MBL-A and MBL-C proteins, but much can be extrapolated from studies of these MBL proteins in other mammals. In addition to complement-dependent activity, MBL also processes complement-independent functions with the ability to inhibit bacterial adhesion (Jack et al. 2005). MBL also acts as an opsonin to enhance bacterial uptake (Kuhlman et al. 1989; Polotsky et al. 1997; Jack et al. 2005). There also seems to be a spectrum of binding of MBL to various bacterial species, with potent binding observed with *S. aureus, Streptococcus pyogenes, Listeria monocytogenes* and non-encapsulated *Neisseria meningitidis* (Levitz et al. 1993; Van Emmerik et al. 1994; Neth et al. 2000), moderate binding observed in *E. coli*, *Haemophilus influenzae* and *Klebsiella* species, and no binding with *Pseudomonas aeruginosa*, *Enterococcus* species and *Streptococcus pneumoniae* (Levitz et al. 1993; Van Emmerik et al. 1994; Neth et al. 2000). Some bacteria have evolved mechanisms to overcome MBL binding, through capsule modifications and sialylation of LPS (Jack et al. 2005; Krarup et al. 2005). MBL is able to bind to several Gram-positive and Gram-negative bacterial ligands, including LPS (*E. coli*, *Salmonella*), peptidoglycan, teichoic acid and lipoteichoic acid (*S. aureus*) (Kuhlman et al. 1989; Polotsky et al. 1996; Nadesalingam et al. 2005a, b; Kurokawa et al. 2016), LAM (*M. avium*) (Polotsky et al. 1997), and mannosylated lipoarabinomannan (ManLAM) (*M. tuberculosis*, *M. bovis*, *Mycobacterium kansasii*, *Mycobacterium gordonae* and *Mycobacterium smegmatis*) (Bartlomiejczyk et al. 2014), and Ag85 (*M. tuberculosis*) (Swierzko et al. 2016). MBL, through opsonization enhances uptake and intracellular killing of *Salmonella* by phagocytes (Kuhlman et al. 1989) and can also inhibit flagellar function, impairing motility which is an important virulence factor (Xu et al. 2016). MBL can also enhance the phagocytosis of mycobacteria and *N. meningitidis* by phagocytes (Polotsky et al. 1997; Jack et al. 2001). MBL can interact with TLR2 in detecting *S. aureus,* and thus, modulate inflammation (Nauta et al. 2003; Ip et al. 2008). All of the above studies suggest that the bovine MBL proteins are likely to have similar activity against these common environmental bacterial pathogens.

There are no reports of activity between bovine MBL and bovine viral pathogens. Undoubtedly, MBL proteins will be involved since that there is considerable data of MBL activity on viral pathogens in other mammalian systems. It would be

particularly prudent to study collectin activity with important viral pathogens of cattle, e.g., those involved in bovine respiratory disease (RBD), such as infectious bovine rhinotracheitis virus (type 1 bovine herpesvirus (BHV1)), parainfluenza virus type 3 (PI3), bovine respiratory syncytial virus (BRSV), as well as bovine viral diarrhoea virus (BVDV), or blue-tongue disease or foot and mouth disease. Nevertheless, MBL has been shown to interact with several human viral pathogens including IAV, where binding of MBL results in the inhibition of viral infectivity (Hartley et al. 1992; Hartshorn et al. 1993b; Reading et al. 1995, 1997). MBL binds to IAV HA and NA antigens (Kase et al. 1999). MBL is able to neutralise HIV-1 *in vitro* targeting gp120 and gp41, and target HIV-infected $CD4^+$ T cells and monocytes and inhibiting reverse transcriptase activity (Ezekowitz et al. 1989; Saifuddin et al. 2000; Teodorof et al. 2014). MBL can activate complement upon binding to gp120 (Haurum et al. 1993). MBL is also able to bind to hepatitis B virus, hepatitis C virus, Ebola virus, flaviviruses such as Dengue and West Nile virus and herpes simplex virus type 1 (Gadjeva et al. 2004; Ji et al. 2005; Brown et al. 2007, 2010; Avirutnan et al. 2011; Fuchs et al. 2011).

Bovine MBL proteins have not been reported to have activity against bovine fungal pathogens. However, there are numerous studies of MBL proteins in other mammals having a significant role in infection and pathogenesis in several relevant fungal pathogens to the bovine host. These include most prominently *Aspergillus* and *Candida* species. MBL is able to bind to *A. fumigatus* (Neth et al. 2000), *B. dermatitidis* (Koneti et al. 2008), *C. albicans* (Kitz et al. 1992; Neth et al. 2000; Ip and Lau 2004; Van Asbeck et al. 2008), *C. parapsilosis* (Van Asbeck et al. 2008), *Pneumocystis* and *C. neoformans* (Chaka et al. 1997; Van Asbeck et al. 2008). MBL binding has been shown to result in fungal aggregation, enhancement of phagocytosis, and complement deposition (Ip and Lau 2004; Kaur et al. 2007; Van Asbeck et al. 2008).

Bovine collectins have not been explored with respect to protozoal and helminth pathogens. Apart from some bovine diseases, Bovidae species can also be reservoirs for zoonotic infections to humans. However, studies are summarised below on MBL from other mammalian species. MBL can bind to the malarial parasite *Plasmodium falciparum* and can activate complement lectin pathway (Klabunde et al. 2002; Garred et al. 2003; Korir et al. 2014). MBL also binds to *Trypanosoma cruzi* and *Leishmania* parasites (Green et al. 1994; Ambrosio and De Messias-Reason 2005; Cestari Idos et al. 2009). In helminth infections, MBL binds to *Schistosoma mansoni* cercariae as well as adult worms and is able to activate the lectin pathway and subsequent complement cascade (Klabunde et al. 2000).

Conglutinin

Conglutinin (CGN) was the first collectin to be discovered in mammals and is uniquely present in Bovidae (Ehrlich and Sachs 1902; Davis 3rd and Lachmann 1984; Hansen and Holmskov 2002). Although initially found in cattle (*Bos taurus*),

CGN has also recently been identified in goat, sheep and other grazing members of the Bovidae genus (Dec et al. 2011). CGN has closely evolved from bovine SP-D, as indicated by its similarity in structure, which facilitates its ability to bind to microbial surface glycoconjugates (N-acetylglucosamine, mannose and fucose) in a Ca^{2+} dependent manner (Loveless et al. 1989; Reid and Turner 1994; Hansen and Holmskov 2002). CGN is predominantly found in the bovine serum and is primarily secreted by the liver at an approximate concentration of 12 μg/mL (Lu et al. 1993a; Holmskov et al. 1998). It is unknown whether CGN is produced locally, e.g., bovine mucosa, but CGN has been detected in splenic, tonsillar, lymphatic and thymic macrophages and dendritic cells (Holmskov et al. 1992) (Table 1). CGN serum levels are heritable, with low calf mortality correlating with high maternal CGN serum levels (Holmskov et al. 1998). CGN has been observed to have anti-microbial properties, but its exact role in the bovine host remains to be properly elucidated. Acute infections, such as pneumonia and metritis are linked with low serum levels of CGN, suggesting predisposition to infection (Ingram and Mitchell 1971; Holmskov et al. 1998). CGN enhances the respiratory burst and reactive oxygen species in bovine granulocytes facilitating enhanced phagocytosis (Dec et al. 2012). Direct binding of CGN to bacterial and viral pathogens has been observed. CGN binds to *Escherichia coli* and *Salmonella typhimurium* (Friis-Christiansen et al. 1990; Friis et al. 1991) and to Gram-negative ligands LPS and peptidoglycan (Wang et al. 1995). CGN has also recently been shown to bind to *Mycobacterium bovis* BCG and other Gram-positive bacteria (Mehmood et al. 2019). CGN can also interact with components of the complement system. CGN binds to C1q receptor and can inhibit the dissociation of Bb from the C3-convertase C3bBb (Malhotra et al. 1990; Tabel 1996). CGN has the unique property of being able to bind iC3b, targeting mannose residues on the iC3b α-chain, but not C3, C3b or C3c (Laursen et al. 1994). Thus, CGN is able to target iC3b bound on cells, resulting in agglutination, such as iC3b-bound erythrocytes (Lachmann and Muller-Eberhard 1968). Furthermore, CGN is able to target and bind to iC3b-bound *E. coli* and facilitate enhancement of the respiratory burst of phagocytes (Friis et al. 1991). CGN is a key component of bactericidal activity in bovine serum (Ingram 1982), and *in vivo*, CGN is able to protect mice experimentally infected with *S. typhimurium* (Friis-Christiansen et al. 1990). In the bovine host, CGN serum levels are lowered during infection, as demonstrated by CGN consumption during *Babesia bovis* infection (Goodger et al. 1981; Ingram 1982). A recombinant truncated fragment of CGN (composed of α-helical neck and the CRD regions only) is able to bind to *M. bovis* BCG and inhibit its uptake by macrophages, with and without prior complement deposition, altering the macrophage inflammatory response (Mehmood et al. 2019). This CGN recombinant fragment also showed bacteriostatic and bactericidal activity against of M. bovis BCG (Mehmood et al. 2019). Thus, CGN seems to target the mycobacterium in two distinct ways: (1) via bacterial lipoarabinomannan (LAM), and (2) in the presence of complement deposition, iC3b (Mehmood et al. 2019). Furthermore, CGN inhibition of mycobacterial uptake by macrophages is probably the result of (1) blocking interaction of mycobacterial LAM with macrophage mannose receptor, and (2) blocking iC3b interaction with macrophage complement

receptors CR3 and CR4 (Mehmood et al. 2019). This study shows important complement-dependent and complement-independent mechanisms of CGN and its involvement in the key interface of host-pathogen interactions in mycobacterial infection and could provide novel avenues for study in bovine tuberculosis, a major infection of cattle in the UK.

CGN has been shown to bind to viral pathogens. CGN binds to the HIV-1 glycoprotein gp160 and inhibits its interaction with the host cell CD4 receptor (Andersen et al. 1991). CGN also acts as an opsonin for IAV, binding to viral hemagglutinin causing viral aggregation and enhanced viral uptake by phagocytes (Hartshorn et al. 1993a). CGN has been shown to inhibit IAV hemagglutination and infectivity and inhibit IAV-mediated neutrophil suppression whilst conversely enhancing neutrophil respiratory burst responses to the virus (Hartshorn et al. 1993a). Interestingly, the CRD of CGN, CL-46 and CL-43 have a greater innate antiviral activity against IAV than human SP-D CRD (Hartshorn et al. 2010a). Moreover, CGN was shown to have a higher inhibitory effect against IAV, than bovine SP-D or CL-43 (Reading et al. 1998). CGN can bind to herpes simplex virus type 2 (HSV-2) and mediate enhancement of infection in mice (Fischer et al. 1994). CGN has been shown to inhibit hemagglutination and infectivity of Newcastle disease virus (Reading et al. 1998), whilst a recombinant truncated fragment of sheep (*Ovis aries*) conglutinin (containing neck and CRD region) was able to reduce bovine herpes virus type I *in vitro* (Mohan et al. 2015). Similar recombinant truncated forms of conglutinin from other Bovidae have also been studied, including goat (*Capra hircus*), buffalo (*Bubalus bubalis*) and nilgai (*Boselaphus tragocamelus*) and were found to have similar reactivities to the full length CGN (Ramesh et al. 2019; Barik et al. 2020).

There are a few studies demonstrating CGN interaction with fungal ligands, which include binding to zymosan and other glycoproteins and polysaccharides from *Saccharomyces cerevisiae* (N-acetylglucosamine, mannose, mannan (Strang et al. 1986; Loveless et al. 1989; Lim and Holmskov 1996). Similarly, the direct binding of CGN to parasites/protozoa is unknown but an early study did report the serum levels of CGN *in vivo* correlating with the severity of Trypanosoma infection (Ingram and Soltys 1960).

CL-43 and CL-46

Like CGN, collectins CL-43 and CL-46 are predominantly serum proteins. CL-43 is synthesised in the liver; the average serum concentration is 21 μg/mL and is structurally similar to CGN and bovine SP-D, and has a preferential ligands similar to that of MBL (Holmskov et al. 1993). CL-43 is in a trimeric structure in the serum and does not form higher order multimeric forms (Holmskov et al. 1995). CL-46 is mainly expressed in the thymus and liver but was also detected in mammary gland and digestive system tissues, although its average serum concentration is not known (Hansen et al. 2002a) (Table 1). It is suggested that CL-46 may be involved in the clearance of apoptotic thymocytes, and there are thymus-related cis-elements

present in its promoter region which may be indicative of T cell mediated CL-46 expression (Hansen et al. 2002a). The carbohydrate preference of the CRD of CL-46 is similar to CGN, suggesting potential iC3b targeting in the thymus, such as the clearance of apoptotic T cells (Uwai et al. 2000) and the development of central tolerance.

The physiological role of CL-43 and CL-46 has not been fully elucidated in the bovine host, but there are a few studies showing their anti-microbial activities *in vitro*. CL-43 has been reported to bind to *E. coli* strain K12, enhancing uptake by phagocytes (Hansen and Holmskov 2002). CL-43 also exhibited significantly higher hemagglutination and inhibition activity against IAV than SP-D, but unlike multimeric forms, CL-43 cannot induce viral or bacterial aggregation (Hartshorn et al. 2002). Although CL-43 did not enhance IAV-induced neutrophil H_2O_2 production, it did strongly enhance neutrophil uptake of IAV, without the need for aggregation (as seen with SP-D) (Hartshorn et al. 2002). CL-43 (like CGN and bovine SP-D) can also bind to bovine rotavirus (Nebraska calf diarrhoea virus), via the VP7 glycoprotein resulting in hemagglutination and neuralisation (Reading et al. 1998). Furthermore, CL-43 showed the highest activity against the virus (Reading et al. 1998). For fungi, CL-43 is can bind to non-capsular forms of *Cryptococcus neoformans in vitro*, inducing agglutination but not with the encapsulated form of the yeast (Schelenz et al. 1995). CL-43 has also been shown to bind to immobilized yeast mannan (Holmskov et al. 1996). For CL-46, the only report of anti-microbial activity is on IAV, where a recombinant fragment (a trimeric neck and CRD) induced aggregation of the virus and strongly enhanced its uptake by neutrophils (Hartshorn et al. 2010b).

CL-L1, CL-K1 and CL-P1

The specific role of these lesser known collectins in the Bovidae is unknown. Nearly all of understanding of the biological role of CL-L1, CL-K1 and CL-P1 has come from human and murine studies. CL-L1 and CL-K1 are present in the blood, forming complexes with mannose-associated serine protease (MASPs) of the lectin complement pathway (Hansen et al. 2010; Axelgaard et al. 2013; Henriksen et al. 2013a; Ma et al. 2013). CL-K1 gene transcripts have been observed mainly in the liver, small intestine, placenta, pancreas, kidney and adrenal, thymus, spinal cord tissues (Keshi et al. 2006) (Table 1). Serum levels of human CL-L1 are approximately 3 μg/mL and for CL-K1 approximately 0.3 μg/mL (Hansen et al. 2010; Yoshizaki et al. 2012; Axelgaard et al. 2013). Another recent study showed the median serum concentration of CL-L1 to be 1.87 μg/mL and CL-K1 to be 0.32 μg/mL (Bayarri-Olmos et al. 2015). For CL-P1, it is in the human umbilical cord plasma at approximately 55–121.4 ng/mL but has not been detectable in adult plasma (Ma et al. 2015). The tissue distribution and serum concentrations of CL-L1, CL-K1 and CL-P1 have yet to be published in the Bovidae. However, there is unpublished data on the Gene Expression Omnibus (GEO) repository showing putative expression of COLEC10,

COLEC11 and COLEC12 in various tissues (NCBI 2020). Circulating CL-L1 and CL-K1 can both form heterotrimers called CL-LK, analogous to C1q globular heads (with a ratio of 2 CL-K1: 1 CL-L1), that can lead to enhanced complement activation via interaction with MASP-2, compared to homotrimers alone (Wong et al. 2008; Axelgaard et al. 2013; Henriksen et al. 2013a; Hansen et al. 2016). Mutations in the COLEC11 gene have been linked with the developmental defect syndrome 3MC (Mingarelli, Malpuech, Michels and Carnevale syndromes) (Carnevale et al. 1989; Rooryck et al. 2011). Serum concentration variability of CL-L1, CL-P1 and CL-K1 and its link with disease is not well understood but increased CL-K1 levels have been linked with the disseminated intravascular coagulation (DIC) condition in humans (Takahashi et al. 2014).

CL-L1, CL-K1 and CL-P1 can bind to various microbes. CL-K1 binds to bacterial and fungal ligands, as well as apoptotic cells (Keshi et al. 2006; Hansen et al. 2010). Murine CL-K1 is able to bind to IAV and reduce its infectivity (Hansen et al. 2010; Henriksen et al. 2013a). CL-K1 also binds DNA and via complement, may be involved in clearance of extracellular DNA, seen from apoptotic cells, neutrophil extracellular traps and biofilms (Henriksen et al. 2013b). CL-K1 can bind to *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *M. tuberculosis* (Keshi et al. 2006; Hansen et al. 2010; Troegeler et al. 2015). CL-P1 can also bind to *E. coli* and *S. aureus* (Ohtani et al. 1999; Jang et al. 2009). Both CL-L1 and CL-K1 can activate the lectin pathway of complement (Henriksen et al. 2013a), whilst CL-P1 can activate the alternative and classical pathways of complement (Roy et al. 2016). The role of CL-L1, CL-K1 and CL-P1 *in vivo* in the bovine host is unknown, but their average serum concentrations seem to be well below that observed for MBL, SP-A, SP-D and CGN, suggesting that these collectins may be more important in local clearance of pathogens and homeostasis. Furthermore, it is still unknown whether CL-L1, CL-K1 and CL-P1 can act as opsonins directly independent of complement deposition. CL-L1 prefers D-mannose, N-acetylglucosamine, D-galactose, L-fucose and D-fructose and binding requires Ca^{2+} (Ohtani et al. 1999; Axelgaard et al. 2013), whilst, CL-K1 prefers L-fucose, D-mannose and N-acetyl mannosamine (Ohtani et al. 1999; Hansen et al. 2010). Interestingly, CL-LK (complex of CL-L1 and CL-K1) has been shown to be a PRR for *M. tuberculosis*, targeting mannose-capped lipoarabinomannan (ManLAM) on the bacterium in Ca^{2+} dependent manner, but not to the related *M. smegmatis* because of a the lack of mannose caps on its LAM (Troegeler et al. 2015). Furthermore, the levels of CL-LK in serum of human tuberculosis patients are lower, compared to controls suggesting that it may be useful as a biomarker for the disease (Troegeler et al. 2015). It would therefore be prudent to examine the correlation of CL-L1, CL-K1, and CL-P1 in *Bos taurus* during mycobacterial infection to ascertain whether these may be useful biomarkers for bovine tuberculosis as well.

Concluding Remarks and Future Directions

The bovine collectins constitute a key component of the innate immune system of cattle, but much of our understanding of their specific biological role in the Bovidae remains unknown. Collectins have been shown to be involved extensively in protection from pathogens and maintenance of homeostasis in several mammalian systems (e.g., human and mice) and similar studies should be conducted in the bovine host with relevant bovine pathogens and other pathological conditions that affect cattle. This is a significant component of bovine immunity that remains unexplored and could be relevant to combatting a number of infectious diseases of cattle, e.g., mastitis, bovine tuberculosis and other bovine respiratory disease and gastrointestinal infections (Fig. 5). Of particular importance is the use of genomic technologies that can be used to further elucidate genetic diversity of bovine collectin genes and other immune markers, to identify traits linked with major diseases of cattle. Such data will allow selective breeding of pathogen-resistant animals and give other insights in how collectins and innate immunity can be bolstered to protect against cattle infection and the reliance of anti-microbial therapy.

Bovine MBL, SP-A and SP-D have been shown to play important roles in bovine innate immunity, but much remains unknown. What remains intriguing is CGN, CL-43 and CL-46, which have evolved from an SP-D ancestral gene, are unique in the Bovidae compared to other mammals. This evolutionary separation is perhaps

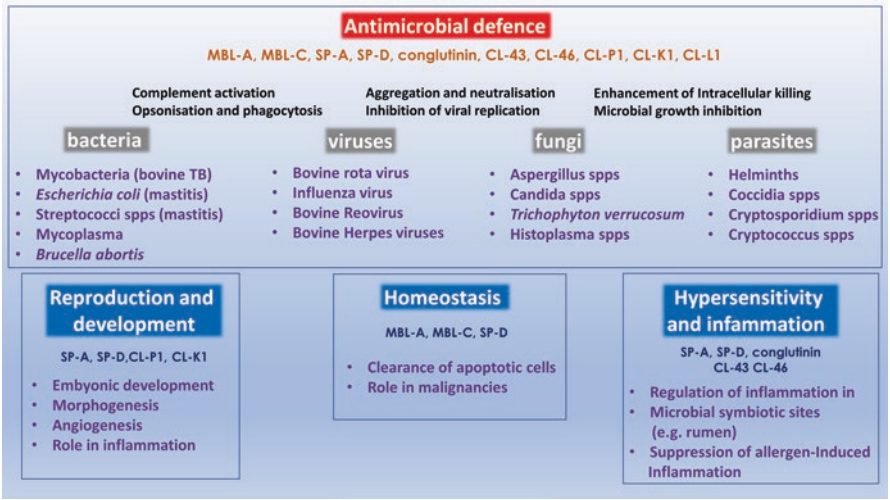

Fig. 5 Putative functions and antimicrobial interactions of the bovine collectins. Summary of the diverse roles of collectins, in antimicrobial defence, reproduction and development, homeostasis and hypersensitivity and inflammation. Note: most of these functions have not been reported in *Bos taurus*, but based on studies in other mammals, the bovine-relevant pathogens and other biological factors that are likely to interact with the bovine collectins in a similar manner. Please consult main body of the review for more details

due to the specific biology of ruminants, which have a high level of microbial symbiosis and thus need a balance of the inflammatory response to prevent tissue damage. These additional collectins may have evolved in this regard to target pathogens in an efficient manner, whilst having anti-inflammatory properties to facilitate microbial symbiosis and prevent tissue damage. Much has still to be learned about the interactions of bovine collectins, (especially CGN, CL-43 and CL-46) with bovine pathogens and in order to understand pathogenesis and susceptibility to infection. Of promise is the use of truncated recombinant forms (CRD and neck region) of some collectins (SP-A, SP-D and CGN) that has shown their potential in antimicrobial prophylaxis or therapy against IAV and tuberculosis (Al-Ahdal et al. 2018; Al-Qahtani et al. 2019; Mehmood et al. 2019). It is hoped that this review will encourage renewed focus and resources in studying bovine collectins more fully, a probable critical arm of bovine innate immunity.

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