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Production and active transport of immunoglobulins within the ruminant mammary gland

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ABSTRACT

The primary function of the mammary gland is to produce milk to feed the suckling young. In ruminants, ingestion of maternal antibodies in mammary secretions facilitates the transfer of passive immunity from mother to young, providing antibody-mediated immunity to protect the neonate against disease while their own immune system develops. Antibodies in mammary secretions also play a role in protecting the gland itself against infection. Here we provide a brief history of studies on immunoglobulins in ruminant mammary secretions and review recent findings describing the mechanisms by which antibody-producing plasmablasts are recruited to the gland and immunoglobulins are transported into ruminant mammary secretions. An improved understanding of the complex interaction of factors which regulate immunoglobulin production and transfer to the ruminant mammary gland may provide opportunities to enhance antibody concentrations in mammary secretions during normal lactation and in response to immunisation. Strategies aimed at increasing antibody concentrations in ruminant mammary secretions have the potential to improve the ability of animals to resist mammary infections, enhance the transfer of passive immunity from mother to young and increase the feasibility of harvesting antibodies from the mammary secretions for use in commercial therapeutic applications for humans and domesticated animals.

1. Introduction

Immunoglobulins (Igs) in ruminant mammary secretions play a central role in active immune protection of the gland against infections, and when transferred to the neonate, provide ongoing passive immune protection to the gastro-intestinal tract of the suckling offspring. In addition, the high concentrations of Igs in bovine colostrum have been commercially exploited to provide nutraceutical and pharmaceutical products for various applications in human health including prevention of travellers' diarrhoea (Travelan®) (www.immuron.com.au, accessed 7th January 2019), improving gut health (Protectyn®) (www.immuron.com.au) and alleviating HIV-associated diarrhoea (ColoPlus® (Floren et al., 2006; www.coloplus.se, accessed 7th January 2019). Scientific interest in enhancing these functions of Igs in mammary secretions is very long standing. The initial empirical studies on vaccination, to stimulate antibody (Ab) protection of the gland, have been augmented over the years by knowledge of selective transport of Igs into mammary sections and the potential for plasmablasts to migrate to the mammary gland from remote sites. Interventions to enhance Ig accumulation in mammary gland secretions could help improve Ig and Ab dependent functions of the gland and commercial exploitation of its products. Here we provide a brief history of studies on Igs in mammary secretions and review recent findings on the mechanisms of Ig transport and plasmablast recruitment to the mammary gland. This review has a specific focus on Ab production and transport in the ruminant mammary gland. For a more comprehensive review of the role of the mammary gland in mucosal and regional immunity across several species see Butler et al. (2015).

2. Immunoglobulins in mammary secretions

The unusual characteristics of first milk have been known through tradition since the earliest times and began to attract scientific investigation in the first half of the 19th Century. From a study of physical properties of bovine colostrum, Davy (1845) concluded that serum constituents were not present in colostrum. With the development of methods for vaccinating animals, the observed phenomenon of transfer of immunity to offspring following natural infection of female goats during pregnancy was replicated experimentally by vaccination of pregnant sheep with anthrax organisms (Chauveau, 1880). The subsequent demonstrations of transfer of immunity from immunised female mice to foster pups contributed to Ehrlich's discovery of Abs in

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1892. By 1912, the high concentration of Ab in goat colostrum and the critical period for absorption of this Ab by the newborn kid had been reported (Famulener, 1912). Commonality of Ab activity in colostrum and blood was subsequently established by Crowther and Raistrick (1916); Howe (1925); Smith (1946) and Larson and Gillespie (1957). Studies with radioisotope-labelled Igs in sheep established that, relative to other Ig isotypes, IgG1 is selectively transported into colostrum (Richards and Marrack, 1962), and that selective transport of this Ig continues at a much reduced rate during normal lactation (Mackenzie and Lascelles, 1968). At the beginning of mammary involution there is a transient increase in the rate of selective accumulation of IgG1 in both ewes and cows (Watson et al., 1972) which ceases in the fully involuted gland. A more detailed understanding of selectivity of Ig accumulation was achieved by expressing the concentration of Igs in serum and mammary secretions as a selective index, corrected for the respective concentrations of each Ig isotype in blood serum (Brandon et al., 1971b), or as an index relative to the concentration of serum albumin in each fluid (Guidry et al., 1980). This approach showed that IgG1, IgG2, IgA and IgM all accumulate in the bovine mammary gland during colostrogenesis with a very high predominance of IgG1 (Watson, 1980). By around the 5th day of lactation there is no further selective accumulation of IgG2, whereas the other Igs continue to selectively accumulate at a lesser rate. During infection or experimental challenge with inflammatory agents, the apparent selective accumulation of Igs decreases (Guidry et al., 1983; Mackie and Logan, 1986; Oestensson and Lun, 2008).

In cattle, the mass of Ig produced in colostrum can differ between breeds (Muller and Ellinger, 1981; Murphy et al., 2005) and tends to increase with lactation number (Pritchett et al., 1991). The mass of IgG1 in colostrum collected at first milking can exceed 2000 g and is positively correlated with colostral volume and with colostral IgG1 concentration but not with the parenchymal mass of mammary tissue (Baumrucker et al., 2010). In addition, both the IgG1 concentration in milk and total mass of IgG1 discharged through milk tend to increase with each lactation up to around the 5th lactation (Liu et al., 2009). Heritable variation occurs in serum Ig concentrations in Holstein Friesian dairy cattle (Mallard et al., 1983) which can influence the availability of Igs for transport and accumulation into colostrum and milk (Fleming et al., 2016). It is also likely that heritable variation occurs in the activity of transport mechanisms and therefore scope may exist to select animals for higher output of Igs in colostrum and milk. This could be a complementary trait to that based on heritable variation in Ab responsiveness to vaccination and infection in ruminants (Wilkie and Mallard, 1999).

Bovine IgE was first identified by observation of homocytotropic Ab in colostrum of cows and in blood of neonates following suckling (Hammer et al., 1971). IgE accumulates in colostrum of cows (Hammer et al., 1971) and ewes (Hine et al., 2010) and is absorbed from the gut of the neonate (Hammer et al., 1971; Pfeffer et al., 2005; Thatcher et al., 1989). In the ewe, it has been shown that accumulation of IgE also occurs in mature milk (Hine et al., 2010).

3. Mechanisms contributing to selective accumulation of Igs in mammary secretions

The high concentration of Ab in colostrum and disparity between the relative concentrations of Ig isotypes in blood and mammary secretion have underpinned interest in the processes that lead to selective accumulation in the mammary gland. Three mechanisms have attracted attention as potentially contributing to this disparity: local production of Igs within the gland, molecular sieving of Igs across the endothelial and epithelial cell barriers that lie between blood and mammary secretions, and active transport of Igs across the same barriers (Guidry et al., 1980; Larson et al., 1980).

3.1. Local production

Controversy over the potential for Ab to be produced locally in the ruminant mammary gland was resolved in the laboratory of Lascelles and colleagues in the 1960s and early 1970s (reviewed by (Lascelles and McDowell, 1974)). Local immunisation of the bovine mammary gland was found to lead to elevated concentrations of Ab (principally IgA and IgM). In addition, systemic priming during mammary involution was found to harness the spontaneous influx of lymphocytes into the gland that occurs at this time and can lead to sustained local Ab production in the subsequent lactation (Watson and Lascelles, 1975). Variations of this protocol have been developed including local boosting of the gland following initial systemic subcutaneous priming (Smith et al., 1999) and intraperitoneal and intramuscular priming, which leads to sustained elevation of IgA Ab titres for commercial production of immune milk in cows (Hodgkinson et al., 2007a). A subset of bovine Abs are known to have an exceptionally long third heavy-chain complementarity-determining region which potentially allows them to interact with recessed epitopes and epitopes on concave surfaces, not normally accessible to other Abs (Stanfield et al., 2018, 2016). This unique characteristic of certain bovine Abs may provide an opportunity for the future development of bovine Abs capable of targeting especially challenging epitopes.

3.2. Molecular sieving and tight junction function

During normal physiological function, proteins in blood diffuse through the vascular endothelium into interstitial fluid in proportions related to their molecular diffusion diameters (Simionescu, 1983). During inflammation, leakage of proteins from the vascular compartment increases due to contraction of endothelial cells (Majno et al., 1969) and temporary disruption of endothelial cell junctions during emigration of inflammatory leukocytes (Issekutz et al., 1980; Wedmore and Williams, 1981). Comparison of Ig concentrations in blood, afferent and efferent mammary lymph, and in milk of mid-lactation cows confirm that Igs entering mammary interstitial fluid from blood undergo differential molecular sieving at the vascular endothelial wall (Oestensson and Lun, 2008). Thus Ig concentrations are lower in interstitial fluid than blood, and relative concentrations in interstitial fluid reflect the molecular size of each Ig isotype (Oestensson and Lun, 2008). Epithelial cells line the mammary gland forming a barrier between the interstitial fluid on the basolateral side of cells and milk in the alveolar lumen on the apical side. Integral to the maintenance of this barrier are the tight junctions (or *zonula occludens*) which surround these epithelial cells, forming a ‘gasket-like’ structure which, when intact, prevents the vectorial movement of small molecules and ions between cells (Stelwagen et al., 1995, 1998). The integrity of tight junctions is maintained throughout the lactation cycle in the healthy mammary gland with the exception of the periparturient and involution periods (Linzell and Peaker, 1974; Fleet and Peaker, 1978). Although increased tight junction permeability during these periods permits the transient movement of small molecules, such as lactose and sucrose, across the epithelium, tight junctions are thought to remain largely impervious to high molecular weight proteins such as Igs. Therefore, selective accumulation of Igs in mammary secretions during colostrogenesis and normal lactation is thought to occur mainly via an active intracellular transport mechanism operating within mammary epithelial cells (Larson et al., 1980) as discussed in detail below.

3.3. Active transport

An active mechanism for selectively transporting Igs from the circulation into mammary secretion during colostrogenesis was first proposed by Brambell (1966). Brambell suggested that proteins were non-selectively taken up by vesicles into mammary epithelial cells and that

those proteins which fail to attach to specific receptors sites in the vesicle wall were selectively degraded prior to being transported across the cell. Based on Brambell's proposed mechanism, serum concentrations of IgG1 and IgG2 were expected to decline in parallel during colostrogenesis. However, a few years' later Brandon et al. (1971b) reported that serum IgG1 concentrations declined sharply in the cow during colostrogenesis, whereas serum IgG2 concentrations remained relatively stable over the same period. Based on this finding, Brandon et al. proposed an alternative hypothesis in which IgG1 is selectively taken up and transported into colostrum by IgG1-specific receptors on the basal or intercellular membrane of mammary epithelial cells. The existence of a receptor which binds the Fc domain of IgG, the neonatal Fc receptor, has since been confirmed in both ovine and bovine mammary epithelial cells (Mayer et al., 2002; Kacskovics, 2004; Mayer et al., 2005; Sayed-Ahmed et al., 2010).

3.3.1. The neonatal Fc receptor

The neonatal Fc receptor (FcRn) was first identified in rodents as the receptor mediating the transfer of maternal Ab from mother to young via the neonatal intestine (Rodewald, 1976; Wallace and Rees, 1980; Rodewald, 1980). In the small intestine of the neonatal rat, FcRn binds maternal IgG in a pH-dependant manner, with binding observed at pH 6.0–6.5 but not at pH 7.4 (Rodewald, 1976, 1980). It is thought that IgG binds to the FcRn expressed on the luminal surface of epithelial cells in the acidic environment of the duodenum and proximal jejunum and the complex is then internalised by receptor-mediated endocytosis and subsequently transported across the cell. Upon reaching the basolateral surface the complex undergoes exocytosis, exposing the complex to a physiologic pH environment which causes it to dissociate, releasing intact IgG into the extracellular fluid beneath the mucosa and thereby facilitating the transfer of maternal Abs from the neonatal intestine into the circulation. More recently, a major role for the FcRn in regulation of serum IgG and albumin homeostasis and IgG-mediated phagocytosis has also been demonstrated (Vidarsson et al., 2006; Cervenak et al., 2011).

The FcRn is thought to play an important role in the selective transport of IgG across the mammary epithelium in several species. In the mouse, accumulation of IgG subclasses in milk is inversely correlated to their affinity for the FcRn, suggesting that in rodents the FcRn may play a dual role, transporting IgG into mammary secretion and also recycling IgG from mammary secretion back into the circulation (bi-directional transcytosis) (Cianga et al., 1999). In contrast to the transport of IgG1 across the intestinal lumen, involving apical to basal transfer from a low pH environment, transport of IgG1 into the mammary gland during colostrogenesis involves basal to apical transfer from a largely pH neutral extracellular environment which does not support the binding of IgG1 to FcRn. Therefore, it has been hypothesised that during colostrogenesis in ruminants, the mammary gland takes up IgG1 from the extracellular environment via fluid phase endocytosis with subsequent acidification in the endosome promoting binding of IgG1 by the FcRn (Baumrucker and Bruckmaier, 2014). Supporting a role for the FcRn in the transfer of maternal IgG into colostrum in ruminants, immunohistochemical studies have demonstrated that both the ovine and bovine FcRn are homogenously distributed within mammary epithelial cells prior to parturition, at a time when IgG1 is rapidly accumulating in the gland, but concentrated on the apical side of the cells following parturition (Mayer et al., 2002, 2005). Associations between the bovine FcRn α-chain gene (FCGRT) alleles and the IgG content of colostrum have been reported, along with corresponding associations in the serum IgG concentration of their newborn calves (Laegreid et al., 2002; Zhang et al., 2009). Associations between FCGRT genotype and IgG concentration in sheep have also been reported (Tian et al., 2015). For a comprehensive review of IgG1 transcytosis during colostrogenesis see Baumrucker and Bruckmaier (2014).

Although it is established that approaching parturition triggers mammary epithelial cells to preferentially bind IgG1 in the ruminant (Kemler et al., 1975; Sasaki et al., 1977; Barrington et al., 1997a), the specific role of the FcRn in selectively transporting IgG subclasses in the ruminant mammary gland remains speculative. In an effort to better understand the function of the FcRn in the ruminant mammary gland, Lu et al. (2007) generated a transgenic mouse model, in which, the bovine FcRn was over-expressed in the lactating mammary gland. Although injection of equal amounts of bovine IgG1 and IgG2 into transgenic mice failed to result in selective accumulation of bovine IgG1 in mammary secretion, the serum to milk ratio of bovine IgG2 (but not IgG1) was higher in transgenic mice than controls. It may be that bovine IgG2 has a higher binding affinity than IgG1 for the FcRn, based on the extended serum half-life of IgG2 in ruminants (Cervenak and Kacskovics, 2009). This suggests that accumulation of bovine IgG subclasses in milk is inversely correlated to their affinity for the bovine FcRn, as in the rodent model (Lu et al., 2007). Based on the molecular weight of FcRn complexes detected in bovine colostral whey, Baumrucker and Bruckmaier (2014) hypothesised that IgG1 is secreted in the bovine mammary gland as a large molecular weight complex composed of three proteins, FcRn, IgG1 and bovine serum albumin (BSA), with each complex containing a single IgG1 and two BSA molecules. Subsequent research by this group has led them to reject this hypothesis based on the finding that the concentration of IgG1 and BSA is not correlated in colostrum. This suggests that in contrast to IgG1, BSA and IgG2 enter colostrum via tight junctions between mammary epithelial cells (Samarütel et al., 2016).

The passive transfer of maternal Abs to the neonate is a two-step process, requiring transfer of Igs into colostrum and subsequent absorption of Igs through the small intestine of the neonate into the systemic circulation. In ruminants, this absorptive process known as the "open gut" mechanism, occurs largely in the first 12 h after birth, after which time, intestinal permeability to colostral Igs in the neonate progressively decreases with gut closure occuring at around 24 h post-birth (Stott et al., 1979). Absorption is mediated by duodenal enterocytes in the small intestine which pinocytotically transport Igs across the intestinal barrier in a non-selective process (Mayer et al., 2002). However, due to the selectivity, which has previously occurred in the mammary gland, colostral Igs absorbed by the neonate ruminant are predominantly of the IgG1 isotype (Brandon and Lascelles, 1971a). Although FcRn transcript expression has been observed in the neonatal intestine of calves, it is not thought to be involved in IgG1 absorption from the intestine (Baumrucker and Bruckmaier, 2014). Investigations have failed to detect expression of FcRn mRNA in the duodenal enterocytes of newborn lambs which absorb intact IgG from colostrum in a non-specific manner (Mayer et al., 2002).

Although the absorption of Ig from the neonatal small intestine appears to be non-selective (Klaus et al., 1969; Halliday et al., 1978), a large proportion of absorbed IgG1 is selectively recycled back into the small intestine of neonatal ruminants in a process mediated by crypt epithelial cells (Newby and Bourne, 1976a; Besser et al., 1988a). In fact, in young calves, IgG1 is the predominant Ig isotype found in secretion of the small intestine, a finding which was thought to explain the favourable correlation observed between passive serum Ab concentration and resistance to diarrheal disease in calves during the first weeks of life (Besser et al., 1988a). It has been reported that circulating IgG1 appears in the gastrointestinal tract of neonatal calves and is effective in preventing infection following challenge with rotavirus (Besser et al., 1988b). Providing further evidence to support a role for the ruminant FcRn in this recycling process, Mayer et al. (2002) observed localised expression of FcRn on the apical side of crypt epithelial cells in the duodenum of newborn lambs, where Newby and Bourne (1976a) had previously detected significant amounts of IgG1. Similar to IgA, ruminant IgG1 is relatively resistant to proteolysis when compared to IgG2, suggesting an important role for IgG1 in the mucosal immunity of ruminants (Newby and Bourne, 1976b; Mayer et al., 2002).

Further functional studies will be required to firmly establish the mechanism by which IgG subclasses differentially accumulate in

ruminant mammary secretions during colostrogenesis and to confirm the role of the FcRn in absorption of maternal Ab from colostrum via the intestinal lumen during the period between birth and 'gut closure' in neonatal ruminants.

3.3.2. The polymeric immunoglobulin receptor

Analogous to the function of the FcRn in transporting IgG, the polymeric immunoglobulin receptor (pIgR) transports IgA across epithelial barriers (Kacskovics, 2004). Transport of IgA, both free and complexed to antigen, across the epithelium is initiated by the binding of IgA to the pIgR expressed on the basolateral surface of mucosal epithelial cells. This complex is then endocytosed and transported across the cell, where upon reaching the apical surface, proteolytic cleavage of the pIgR results in the release of IgA into the lumen (Kaetzel et al., 1991). Proteolytic cleavage of the pIgR results in the ectoplasmic domain of pIgR, also known as secretory component (SC), to remain bound to the secreted IgA. This IgA-SC complex is commonly known as secretory IgA (sIgA). The pIgR is transported across epithelial cells and cleaved at the apical surface whether or not Ig is bound, thereby resulting in the release of both free and Ig-bound SC into the lumen. Secretory component acts to stabilise Igs in the lumen environment by increasing their resistance to degradation by proteases present in secretion (Underdown and Dorrington, 1974) and ensures appropriate tissue localisation of sIgA by anchoring Ab to the mucosal lining of the epithelial surface (Phalipon et al., 2002; Phalipon and Corthesy, 2003).

The pIgR selectively transports polymeric Igs (Kaetzel et al., 1991) and although the pIgR primarily functions to transport dimeric IgA, this receptor also functions to transport pentameric IgM across the epithelial barrier (Mostov, 1994). Selectivity for polymeric Igs is based on the presence of J-chain, a small polypeptide present only in polymeric Igs. J-chain plays an essential role in stabilising formation of the IgA-SC complex and promoting effective pIgR-mediated transport across the epithelium (Hendrickson et al., 1996; Johansen et al., 1999; Johansen et al., 2001).

Studies using gene knockout mice have demonstrated that active IgA and IgM transport into external secretions does not occur in mice lacking a functional pIgR, suggesting that pIgR-mediated transport of polymeric Igs across the epithelium is a non-redundant mechanism in the mouse (Johansen et al., 1999). Furthermore, production of pIgR in the murine mammary gland has been shown to be the limiting factor in the transport of IgA into milk under normal non-inflammatory conditions (De Groot et al., 2000).

The bovine pIgR was first characterised by Kulseth et al. (1994). Around the same time, Verbeet et al. (1995) reported localised expression of pIgR mRNA in the bovine mammary gland, liver, lung, kidney and intestine, with the highest level of expression observed in the mammary gland. Expression of pIgR mRNA has also been reported in the ovine mammary gland (Rincheval-Arnold et al., 2002a) with low level expression during the first two trimesters of pregnancy which increases to a higher level during the last trimester. Accumulation of pIgR transcripts further increased three days post-parturition and reached the highest levels observed at 70 days into lactation. Supporting a role for the pIgR in secretion of IgA into the ruminant mammary gland, Berry et al. (2013) reported polymorphisms in the bovine pIgR gene account for more than 25% of the phenotypic variation in colostrum IgA concentration observed between animals. Based on these findings it was proposed that genetic selection based on polymorphisms in the pIgR gene might generate herds producing milk with increased IgA concentrations. Although expression of pIgR mRNA has been confirmed in the ruminant mammary gland, further functional studies are required to confirm the role of pIgR in transporting polymeric Igs across the mammary epithelial barrier in ruminants.

3.3.3. Is there a receptor mediating IgE transport?

Extrapolating from observations in rodents, it was proposed that the low-affinity IgE receptor (CD23) may play a role in the transport of IgE across the mammary epithelium in ruminants (Pfeffer et al., 2005). IgE is selectively transported into ovine mammary secretions and expression of CD23 mRNA in the ovine mammary gland reflects the concentration of IgE in mammary secretions during the various stages of the lactation cycle (Hine et al., 2010). These findings suggest a role for CD23 in the transport of IgE across the mammary epithelium in ruminants. However, further functional studies will be required to confirm the role of CD23 in IgE transport in the ruminant.

3.3.4. Regulation of Fc receptor expression

In view of the receptor-mediated transport mechanisms described above, it is important when developing strategies to enhance Ig levels in mammary secretions that availability of receptors that mediate Ig transport be considered. Ig transport by mammary epithelial cells is thought to be directly or indirectly regulated by a range of soluble factors including cytokines and hormones (Lascelles and McDowell, 1974). Barrington et al. (1997b) demonstrated that prolactin, the principal hormone responsible for suppression of colostrogenesis and initiation of lactogenesis, reduces IgG1 receptor activity in mammary tissue explants from cows producing colostrum. These researchers went on to demonstrate that *in vivo* administration of recombinant bovine prolactin to cows, induced into colostrogenesis using hormonal treatment, increased lactogenic activity, decreased IgG1 receptor expression and decreased IgG1 levels in the mammary gland (Barrington et al., 1999). In humans, cytokine modulation of FcRn expression has been reported with tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) being shown to induce upregulation and downregulation respectively, of FcRn expression in various cell types (Liu et al., 2007, 2008).

Rincheval-Arnold et al. (2002a) investigated the endocrine regulation of pIgR expression in the ovine mammary gland during pregnancy and lactation and hypothesised that the enhancement of pIgR expression observed in the mammary gland during lactation is a consequence of the combined effects of increased levels of prolactin and glucocorticoids. Subsequent *in vitro* studies using cultured ovine mammary epithelial cells have demonstrated that treatment of cells with a combination of prolactin and glucocorticoids alone are not sufficient to induce strong expression of pIgR mRNA. Strong expression was only achieved when interferon gamma (IFN-γ) was co-administered with prolactin and glucocorticoids, suggesting a co-operative effect of circulating hormones and locally produced cytokines in the regulation of pIgR expression in the ovine mammary gland (Rincheval-Arnold et al., 2002b). In fact, pro-inflammatory cytokines including IFN-γ, tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), along with cytokines characteristic of multiple T cell lineages including Th1, Th2 and Th17, have been shown to upregulate pIgR expression in a variety of species and cell types (Baker et al., 2015). Interestingly, the Th1-type cytokine IFN-γ and the Th2-type cytokine IL-4, which often have antagonistic effects, act synergistically to upregulate pIgR expression (Phillips et al., 1990). Furthermore, IFN-γ appears to have contrasting regulatory effects on Fc receptor expression in various cell types, acting to downregulate FcRn expression and upregulate pIgR expression (Phillips et al., 1990; Liu et al., 2007, 2008). It has been hypothesised that responsiveness of the pIgR gene to such a diverse array of cytokines may have conferred an evolutionary advantage by enhancing the transport of IgA to mucosal sites in response to a wide range of immune stimuli (Baker et al., 2015).

4. Plasma cell recruitment to mucosal sites

The role of epithelial transport mechanisms in mediating accumulation of Igs in mammary secretions discussed above suggests that the concentration of Igs in interstitial fluid should influence ultimate concentrations in secretions. Therefore, there is interest in understanding the mechanisms that influence recruitment of plasmablasts into the gland as a source of local production of Igs. Leukocyte migration from

blood into both lymphoid and non-lymphoid tissue requires a highly orchestrated cascade of adhesion and signalling events (Steebar et al., 2005). This process is mediated by a combination of adhesion and chemoattractant molecules, which interact with specific receptors on the surface of circulating cells, triggering their extravasation through the endothelium and subsequent migration into specific target tissues. Specificity of this migration process is maintained through the expression of unique combinations of adhesion and chemoattractant molecules in target tissues and cognate receptors on circulating cells.

The extravasation of circulating leukocytes from blood vessels is a multi-step process involving a cascade of adhesive and activation events. Circulating leukocytes tether and roll on the endothelium through transient selectin-carbohydrate ligand and/or integrin-adhesion molecule ligand interactions. Rolling allows leukocytes to sample the endothelium for signals (such as chemokines) which activate integrins on the cell surface and trigger firm adhesion. Further signals direct adherent leukocytes to migrate across the endothelium into the extravascular space. Once in the extravascular space they proceed to migrate along chemokine concentration gradients to their target tissues (Fabbri et al., 1999; Kunkel and Butcher, 2003).

Plasmablasts generated in germinal centres can locally differentiate into plasma cells, remaining sessile in their secondary lymphoid tissue of origin, or they can exit the secondary lymphoid tissue via efferent lymph and subsequently populate distant sites. The homing potential and final tissue distribution of Ab secreting B cells (ASCs) is influenced by both the Ig isotype they express and the site at which their cognate antigen was encountered. This non-random distribution provides evidence for at least some level of compartmentalisation within the common mucosal system (Kunkel and Butcher, 2003). Studies in humans and mice have revealed that IgA and IgG ASCs have distinctive trafficking patterns within the body. IgA ASCs, which mainly arise in mucosal lymphoid tissues, display trafficking patterns which are dependent on their site of induction. In contrast, the trafficking patterns of IgG ASCs to the bone marrow and sites of inflammation are largely independent of their site of induction (reviewed in Kunkel and Butcher, 2003).

In humans and mice, the migration of IgA ASCs from their sites of induction to target tissues is largely coordinated by the chemokines, thymus-expressed chemokine (TECK/CCL25) and mucosae-associated epithelial chemokine (MEC/CCL28) together with the tissue-specific adhesion molecules, mucosal addressin cell-adhesion 1 (MAdCAM-1) and vascular cell-adhesion molecule (VCAM-1) (Kunkel and Butcher, 2003). Expression of CCL25 is highly restricted to the small intestine in humans and mice where it acts as an attractant for lymphocytes expressing the chemokine receptor, CCR9 (Kunkel et al., 2000; Bowman et al., 2002). Similarly, MAdCAM-1 is selectively expressed in the intestinal lamina propria and intestinal lymphoid tissues, where it acts as an attractant for lymphocytes expressing the integrin, α4β7 (Butcher et al., 1999). Expression of CCR9 and α4β7 is induced during the development of IgA ASCs in intestinal lymphoid tissues, allowing these cells to home back to their site of induction (Kunkel and Butcher, 2003).

It is common for intestinally derived IgA ASCs in humans and mice to co-express CCR9 and CCR10 chemokines receptors along with α4β7 and α4β1 integrins (Kunkel and Butcher, 2003). The CCR10 chemokine ligand, CCL28, and the α4β1 adhesion molecule ligand, VCAM-1, are expressed in a diverse range of mucosal sites including the mammary gland, salivary gland, colon, lung and trachea, thereby allowing intestinally derived IgA ASCs to traffic both to intestinal and non-intestinal mucosal sites. This process contributes to the dissemination of IgA ASCs throughout the mucosal immune system in humans and mice, the hallmark feature of the common immune system (Kunkel and Butcher, 2003; Lazarus et al., 2003). In contrast to IgA ASCs derived from the intestine, IgA ASCs induced in non-intestinal mucosal sites such as the lungs, do not express CCR9 and as a consequence do not traffic to the small intestine (Kunkel and Butcher, 2003).

4.1. Plasma cell homing to the mammary gland

Significant numbers of IgA ASCs migrate to the murine mammary gland during late pregnancy and early lactation, a proportion of which originate from gut-associated lymphoid tissue (GALT), supporting the concept of a common mucosal system (McDermott and Bienenstock, 1979). Breast milk sIgA has been shown to exhibit specificity for common intestinal and respiratory pathogens suggesting the mammary gland forms part of a common mucosal system in humans also (Goldman, 1993; Brandtzaeg, 2010). Early studies in mice demonstrated that MAdCAM-1 is expressed by venule endothelium cells in the mammary gland with expression peaking during late pregnancy, declining during early lactation, and plateauing in mid to late lactation (Tanneau et al., 1999; van Der Feltz et al., 2001). In contrast, numbers of $\beta7^+$ IgA ASCs in the murine mammary gland increase during mid to late lactation, suggesting that expression of MAdCAM-1 is not the rate-determining factor governing recruitment of IgA ASCs to the gland and that other factors, such as chemoattractants, may play a critical role in the recruitment process (Tanneau et al., 1999; van Der Feltz et al., 2001; Nishimura, 2003).

More recently, a critical role for CCL28, as the chemokine signal invoking recruitment of IgA ASCs to the murine mammary gland, has been demonstrated (Wilson and Butcher, 2004; Morteau et al., 2008). Expression of CCL28 is up-regulated in the murine mammary during lactation and IgA ASCs isolated from the murine mammary gland have been found to express CCR10 and migrate effectively to CCL28 *in vitro* (Wilson and Butcher, 2004). Furthermore, the *in vivo* treatment of mice with anti-CCL28 Ab blocks IgA ASC accumulation in the gland which in turn inhibits IgA Ab secretion in milk and subsequent uptake of maternal IgA by the neonate (Wilson and Butcher, 2004). Supporting this finding, Morteau et al. (2008) demonstrated in knockout mice that CCR10 deficiency impairs IgA ASC accumulation in mammary secretions and passive transfer of maternal Ab to the neonate.

Expression of the adhesion molecules, VCAM-1 and glycosylation-dependent cell-adhesion molecule 1 (GlyCAM-1), a mucinlike endothelial glycoprotein that acts as a ligand for L selectin, have also been detected in the lactating murine mammary gland (Dowbenko et al., 1993; Tanneau et al., 1999; Kunkel and Butcher, 2003). In mice, the GlyCAM-1 protein is expressed by mammary epithelial cells during normal lactation and is also found in the milk of the secreting mammary gland. However, the form of GlyCAM-1 found in murine milk is unable to interact with L selectin, suggesting a function additional to cell adhesion in the mammary gland (Dowbenko et al., 1993). Although VCAM-1 is also expressed in the murine mammary gland, expression was only detected on large blood vessels and not on smaller vessels where lymphocyte extravasation occurs (Tanneau et al., 1999). Although such a distribution pattern suggests a limited role for VCAM-1 in the recruitment of ASCs to the mammary gland, a recent study has demonstrated that the interaction of VCAM-1 and α4β1 but not MAdCAM-1 and α4β7 is crucial for effective migration of IgA ASCs to the lactating murine mammary gland (Low et al., 2010). Despite this role for VCAM-1 and CCL28, it has been suggested that their level of expression in the murine mammary gland, like that of MAdCAM-1, is not the rate-limiting factor in ASC migration, as expression occurs at levels in excess of that required to facilitate effective ASC migration (Boumahrou et al., 2012).

Vascular adhesion molecule and chemokine expression patterns in the mammary gland of other monogastric species such as the pig have also been investigated. In agreement with observations in the mouse, CCL28, VCAM-1 and MAdCAM-1 expression is up-regulated in the porcine mammary gland during late gestation and into lactation (Meurens et al., 2006; Berri et al., 2008; Bourges et al., 2008). This increase in expression coincides with an increase in the number of IgA ASCs (including $\alpha4\beta7^+$ and $\alpha4\beta1^+$ IgA ASCs) in the gland, suggesting that the recruitment of IgA ASCs to the porcine mammary gland is

mediated by VCAM-1/α4β1 and MAdCAM-1/α4β7 interactions in conjunction with CCL28/CCR10 interactions (Bourges et al., 2008). Although CCL28 mediates the trafficking and accumulation of cells expressing both CCR3 and/or CCR10 receptors, the expression pattern of CCR10, but not CCR3, transcripts correlated with CCL28 expression and the accumulation of IgA ASCs in the mammary glands of sows suggesting CCL28/CCR10 interactions are important for IgA ASC trafficking to the mammary gland in pigs (Berri et al., 2014).

Comparatively less is known about the chemokines and adhesion molecules which mediate ASC recruitment to the ruminant mammary gland. Studies in sheep have shown that expression of CCL28 mRNA progressively increases in the mammary gland during gestation, while CCL25 mRNA is expressed at only extremely low levels throughout the gestation period (Meurens et al., 2007). Similarly in cattle, high levels of CCL28 (but not CCL25) mRNA expression have been reported in the mammary gland at non-defined stages of the lactation cycle (Distelhorst et al., 2010). Expression of CCR10 mRNA has also been detected in both the ovine and bovine mammary gland. However, expression levels in bovine tissues were low relative to expression levels in the small intestine (Meurens et al., 2007; Distelhorst et al., 2010).

Following ingestion by the neonate, maternal leukocytes present in ruminant colostrum, can cross the intestinal epithelium of the neonate and enter the circulation (Schnorr and Pearson, 1984; Liebler-Tenorio et al., 2002). Subsequently, antigen-specific colostral lymphocytes can reside in neonatal lymphoid tissue until activated by cognate antigen (Donovan et al., 2007). Following activation these cells can enhance neonatal immunity during early life and impart immunological memory to the neonate (Tuboly et al., 1995). The role of colostral cells in the development of the neonatal immune system in ruminants has been reviewed extensively elsewhere (Gonzalez and Dus Santos, 2017).

Investigations into the expression profiles of homing receptors on lymphocyte subsets in the milk and blood of dairy cattle during the periparturient period have shown that twice as many milk lymphocytes express L-selectin as compared to α4β7 (Harp et al., 2004). This suggests that the bovine mammary gland is more closely linked to the peripheral, rather than the mucosal immune system. Supporting this notion, Hodgkinson et al. (2007b) reported that MAdCAM-1 expression could not be detected in bovine mammary tissue during the various stages of the lactation cycle, pregnancy, colostrogenesis, lactation and involution. Analysis at the transcript level showed that MAdCAM-1 is expressed more than 5×10^3-fold lower in bovine mammary gland, compared to Peyer's patch tissue. Based on expression profiles of homing receptors on milk lymphocytes, expression levels and distribution patterns of VCAM-1 and peripheral node addressin (PNAd) were also investigated in the study. In contrast to MAdCAM-1, VCAM-1 expression was detected in the mammary gland during both colostrogenesis and lactation, with peak expression levels observed during colostrogenesis. However, the tissue distribution of VCAM-1, which was restricted to the perimeter of secretory alveoli and large venules, suggested that it is not involved in the recruitment of lymphocytes to the bovine mammary gland. The term PNAd refers to a set of antigens including the sulphated L-selectin ligands, CD34, GlyCAM-1 and a subset of MAdCAM-1 (Streeter et al., 1988). PNAd was detected in supramammary lymph node tissue during all stages of the lactation cycle, but was not detected in bovine mammary gland tissue at any stage tested (Hodgkinson et al., 2007b). These researchers then went on to investigate adhesion molecule expression induced in the bovine mammary gland in response to intra-mammary immunisation. Results showed that neither MAdCAM-1 nor PNAd could be detected in the alveolar mammary tissue of immunised or control glands following immunisation. Although VCAM-1 expression was detected in the mammary gland, tissue distribution was restricted to larger venules and expression levels did not differ significantly between immunised and control glands (Hodgkinson et al., 2009). Expression of both VCAM-1 and PNAd was observed in supramammary lymph node tissue. However, expression levels in nodes draining immunised and control glands also did not differ significantly (Hodgkinson et al., 2009). Together, these results suggest that adhesion molecules mediating the trafficking of lymphocytes to the ruminant mammary gland differ from those in other species, supporting the hypothesis that immune responses of the ruminant mammary gland have the characteristics of peripheral tissues, in contrast to mammary gland responses of monogastric mammals that follow the mucosal pattern (Salmon et al., 2009). Thus further studies are required to fully elucidate the cascade of adhesion and signalling events which orchestrate plasma cell homing to the ruminant mammary gland during the lactation cycle.

4.2. Regulation of chemokine and vascular adhesion molecule expression in the mammary gland

Mammotropic hormones are thought to play an important role in regulating the recruitment of ASCs to the mammary gland. Early studies demonstrated that co-administration of progesterone, oestrogen and prolactin to virgin female mice significantly increased both the number of IgA ASCs and the amount of intra-epithelial IgA in the mammary gland (Weisz-Carrington et al., 1978). Based on these findings, it was hypothesised that IgA ASCs likely express a cell-surface 'element' capable of interacting with tissue receptors; however, the nature of the 'element', and the receptors involved were unknown at the time. Following subsequent characterisation of these cell surface elements and tissue specific receptors which play an important role in orchestrating the trafficking of ASCs to mucosal compartments within the body, factors which influence their expression have been investigated. Evidence that hormones may play a role in regulating the expression of adhesion molecules important for ASC trafficking was provided when an oestrogen receptor binding site was discovered upstream of the transcription start site in the gene encoding murine MAdCAM-1 (Sampaio et al., 1995). Subsequently, it was demonstrated that 17β-estradiol and prostaglandin E_2 stimulate expression of VCAM-1 in cultured human endothelial cells (Winkler et al., 1997) and expression of GlyCAM-1 was found to closely parallel changes in progesterone receptor expression in the ovine uterus, suggesting a role for progesterone in the regulation of GlyCAM-1 expression (Spencer et al., 1999). This led Hou et al. (2000) to investigate hormonal regulation of GlyCAM-1 in the murine mammary gland where progesterone was shown to suppress GlyCAM-1 expression, while prolactin, in combination with other factors, induces GlyCAM-1 expression. This finding is supported by the observation that GlyCAM-1 expression is upregulated in the murine mammary gland during lactation when prolactin levels are high and progesterone levels are low (Hou et al., 2000). Expression of chemokines involved in recruitment of ASCs to the mammary gland are also thought to be influenced by the hormone environment. Prolactin has been shown to upregulate CCL28 expression in the murine mammary gland. However failure of prolactin to upregulate CCL28 expression *in vitro* suggests additional factors, present *in vivo,* are required for prolactin to exert its influence (Hyde, 2007). Oestrogen has also been shown to regulate CCL28 expression. By blocking oestrogen function through administration of an oestrogen antagonist, Cha et al. (2011) demonstrated that oestrogen directly regulates CCL28 expression in the uterus of mice and subsequently influences migration of IgA ASCs following mucosal vaccination.

Although expression of MAdCAM-1 does not appear to be induced in non-mucosal sites of acute inflammation, the pro-inflammatory cytokines TNF-α and IL-1 have been shown to induce expression of MAdCAM-1 in a concentration-dependant manner in cultured murine endothelial cells (Sikorski et al., 1993). As VCAM-1 was first identified as a protein expressed on endothelial cells following stimulation with pro-inflammatory cytokines (Osborn et al., 1989), it is not surprising that expression of this adhesion molecule is also induced in a concentration-dependant manner by TNF-α and IL-1 (Sikorski et al., 1993). In contrast, IFN-γ enhances TNF-α and IL-1 induced expression of VCAM-1 but suppresses TNF-α and IL-1 induced expression of

MAdCAM-1 in cultured murine endothelial cells (Sikorski et al., 1993).

The effect of age and pregnancy status on immune responses in dairy heifers has been reported previously with results demonstrating that responses became increasingly type 1 biased as heifers approached twelve months of age, from which point responses then became increasingly type 2 biased with age and length of gestation (Hine et al., 2011). Supporting this notion, cytokine profiles of $CD4^+$ lymphocytes isolated from the blood of dairy cows within three days of calving suggest that these cells act predominantly as Th2, rather than Th1, effector cells at that time (Shafer-Weaver et al., 1999). Further research is required to improve our understanding of the combined effects of periparturient hormonal and Th cell differentiation changes on the expression of molecules involved in the homing of plasma cells to the ruminant mammary gland.

5. Strategies to increase antibody concentrations in mammary secretions

An improved understanding of the complex interaction of factors which regulate Ab production and transfer to the ruminant mammary gland may provide opportunities to enhance Ab concentrations in mammary secretions during normal lactation and in response to immunisation.

Successful vaccine development is reliant on the ability of vaccines to generate protective responses at their target site. While systemic vaccination provides a practical route for vaccine administration, generating strong responses to vaccination at target mucosal sites following systemic vaccination can be challenging. Knowledge of the role that chemokines play in orchestrating the trafficking of immune cells to mucosal sites provides opportunities for these messenger molecules or synthetic molecules which can mimic their action, to be used as vaccine adjuvants to improve induction of responses at target mucosal sites. Indeed, there are numerous examples in the literature describing the successful use of chemokines as adjuvants when targeting mucosal sites with vaccination. For example, both CCL25 and CCL28 have been used successfully as DNA vaccine adjuvants to enhance vaccine responses at mucosal sites following systemic administration in mice (Kutzler et al., 2010; Kathuria et al., 2012). In these studies, co-delivery of chemokines and vaccine antigens were shown to induce infiltration of cells expressing cognate chemokine receptors to the site of vaccination, thereby influencing the subsequent trafficking patterns of stimulated cells and enhancing IgA responses at mucosal sites. The adjuvant potential of chemokines have also been investigated in virus-like particle (VLP) vaccines. Co-delivery of CCL28 and influenza HA antigens in chimeric VLPs to mice has been shown to significantly enhance both systemic IgG and mucosal IgA responses (Mohan et al., 2016). The development of effective vaccines to protect the ruminant mammary gland against the major mastitis-causing pathogens has been a major research focus for many years now; however, very few products have progressed to commercialisation (Rainard et al., 2018). Although effective mastitis vaccines are very appealing, both in terms of preventing intramammary infections and also reducing antibiotic use, current vaccine technologies have largely failed to stimulate sufficiently robust humoral and cell-mediated immune responses to completely protect the host from infection or successfully clear pathogens in the early stages of infection (Rainard et al., 2018). The use of chemokine adjuvants has potential to improve the efficacy of vaccines targeted at protecting the ruminant mammary gland. However, the fact that the ruminant mammary gland does not appear to form part of a common mucosal system will continue to provide unique challenges for researchers.

Increasing basal Ab levels in ruminant mammary secretions would potentially have significant benefits for protection of the mammary gland and the suckling neonate. Intramammary infusion of immunomodulating agents known to induce inflammation can protect the gland against infection. For example, pre-treatment of cows with lipopolysaccharide via the intramammary route has been shown to be effective in minimising the severity of clinical signs associated with mastitis when artificially challenged up to 10 days post treatment (Petzl et al., 2012). The potential for intramammary devices to protect the gland against common mastitis-causing pathogens has also been investigated in dairy cattle with variable success (Schultze and Paape, 1984; Paape et al., 1988). In the case of biological immunomodulating agents, although several of these agents have been shown to be effective at providing protection for the mammary gland against infection, protection is generally short term. Any increase in Ab concentrations in mammary secretions as a result of treatment is also likely to be transient. In contrast, more sustained local Ab production can be achieved in the ruminant mammary gland using specific vaccination protocols, but such protocols require multiple systemic priming vaccinations prior to local boosting of the mammary gland (Hodgkinson et al., 2007a).

Genetic selection has the potential to permanently increase Ab concentrations in ruminant mammary secretions. Methods have been developed to assess the immune competence of pigs, dairy cattle and beef cattle, which combine measures of an animal's ability to mount both Ab- and cell-mediated immune responses (Wilkie and Mallard, 1999; Thompson-Crispi et al., 2012; Hine et al., 2014; Aleri et al., 2015). Results from these studies suggest that large variation exists in the ability of individual animals to mount immune responses within a herd or group of animals and that immune competence traits are moderately heritable, suggesting reasonable genetic gains can be expected when selecting for immune competence (Wilkie and Mallard, 1999; Thompson-Crispi et al., 2012; Hine et al., 2014). Studies in dairy cows have further demonstrated that animals, identified as high Ab-mediated immune responders, based on antigen-specific serum Ab responses to antigens, have higher concentrations of total IgG in their colostrum relative to their average and low immune responder counterparts, with 84% of high, 69% of average and 68% of low responder animals having IgG Ab concentrations in colostrum exceeding 5 g/dL (Fleming et al., 2016). Polymorphisms in the genes encoding the FcRn α-chain gene (FCGRT) and the pIgR gene have also been associated with increased concentrations of IgG1 in bovine and ovine colostrum (Zhang et al., 2009; Tian et al., 2015) and increased IgA concentrations in bovine milk (Berry et al., 2013). Therefore selection for immune competence, in conjunction with selection for specific Fc receptor gene alleles, may provide a strategy to significantly enhance Ig concentrations in the mammary secretions of ruminants.

Combining genetic selection with the employment of targeted management procedures, such as boost vaccination of animals in late pregnancy, is expected to maximise the potential of increasing Ig concentrations in the ruminant mammary gland. Such strategies are expected to improve the ability of animals to resist mammary infections, enhance the transfer of passive immunity from mother to young and increase the feasibility of harvesting Abs from the mammary secretions of ruminants for use in commercial therapeutic applications.

Declarations of interest

None.

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