

Review article

The IgA system: a comparison of structure and function in different species

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Abstract – The predominant immunoglobulin isotype on most mucosal surfaces is secretory immunoglobulin A (SIgA), a polypeptide complex comprising two IgA monomers, the connecting J chain, and the secretory component. The molecular stability and strong anti-inflammatory properties make SIgA particularly well suited to provide protective immunity to the vulnerable mucosal surfaces by preventing invasion of inhaled and ingested pathogens. In contrast to SIgA, IgA in serum functions as an inflammatory antibody through interaction with Fc α R on immune effector cells. Although IgA appears to share common features and protective functions in different species, significant variations exist within the IgA systems of different species. This review will give an overview of the basic concepts underlying mucosal IgA defence which will focus on the variations present among species in structure, antibody repertoire development, pIgR-mediated transport, colostrum IgA content, hepatobiliary transport, and function with particular emphasis on the IgA system of the pig and dog. These interspecies variations emphasise the importance of elucidating and analysing the IgA system within the immune system of the species of interest rather than inferring roles from conclusions made in human and mouse studies.

IgA / polymeric IgR / Fc α R / mucosal antibodies / domestic animals

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1. INTRODUCTION

IgA, in the form of secretory IgA (SIgA) is the major antibody isotype present in

mucosal secretions and has many functional attributes, both direct and indirect, serving to prevent infective agents such as bacteria and viruses from breaching the mucosal

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barrier. The mucosal predominance of this antibody isotype depends on a cooperation between local plasma cells that produce polymeric IgA (pIgA) and mucosal epithelial cells that express the polymeric Ig receptor (pIgR). After release from the plasma cells and diffusion through the stroma, pIgA become bound to pIgR, after which it is transported across mucosal epithelial cells for extrusion into external secretions after cleavage of pIgR. IgA is also present in serum where it functions as an inflammatory antibody through interactions with Fc α R on immune effector cells. This review details current understanding of the structural and functional characteristics of IgA, the antibody repertoire development, pIgR-mediated IgA transport into mucosal secretions, hepatobiliary IgA transport, colostral IgA content, and adhesion molecules and factors determining the homing of IgA⁺B cells to the mucosa and driving terminal differentiation into IgA⁺ plasma cells. Furthermore, the differences existing among domestic animals within the IgA system are highlighted, with particular emphasis on the IgA system of the pig and dog. In addition, attention is given to other antibody isotypes present in the mucosa.

2. STRUCTURE OF IgA

Although IgA appears to share common protective functions in different species, variation in gene number, allotypes and molecular forms have been noted. In humans, two IgA heavy constant region (C α) genes are present, giving rise to two IgA subclasses, IgA1 and IgA2. On the contrary, in pigs only one C α gene [16] is present which occurs in two allelic forms that differ in hinge length [19]. Both forms appear well represented in swine populations and segregate as co-dominant Mendelian alleles. A single C α gene has been described in dogs [78] which occurs in four allelic forms differing in the length of the hinge region [79]. The distribution of allelic forms within the dog population is breed

specific since some types of pedigree dog had a single allelic form within them¹. Whether or not the allelic forms of IgA present in pigs and dogs differ in function because of structural differences in their hinge region remains to be determined. The sequence of porcine IgA, with exception of the hinge, is most homologous with human IgA, followed by mouse and rabbit IgA [16].

Humans and mice generate the bulk of Ig diversity through the rearrangement of multiple V(D)J gene segments [2, 59]. Additional diversity can be generated junctionally and through terminal deoxynucleotidyltransferase additions [52]. Swine have < 20 V_H genes, a single J_H and perhaps a limited number of D_H segments [21]. Newborn piglets show preferential V_H and D_H usage and may use gene conversion as a mechanism for expanding their antibody repertoire. Consequently, swine rather belong to the group of animals that includes rabbits, chickens, sheep and cattle when classified on the basis of B cell development, despite the close similarity of their Ig gene sequences to humans. This group, unlike rodents and humans, has a single V_H family and uses lymphoid follicles associated with the lower gut early in life (rather than bone marrow throughout life) to diversify their antibody repertoire via gene conversion as well as somatic hypermutation [20, 21, 55, 94, 95]. Indeed, in the pig, different Peyer's patches (PP) are present [10]. The jejunal PP (JPP) are distributed as discrete patches along the jejunum and proximal ileum and persist throughout life. On the contrary, the ileal PP (IPP) occurs as a continuous patch, commencing near the ileo-caecal junction and extending for up to 2 m along the terminal ileum but shrinks within a year to form discrete patches. In contrast to the JPP, the porcine IPP has characteristics of a primary lymphoid organ (in comparison with the JPP, low lymphocyte migration, smaller interfollicular regions,

¹ Peters et al., unpublished data.

higher incidence of B cells [6, 10] and identification of the majority (> 90) of follicular cells as apoptosis-sensitive immature B cells [3]). However, the use of gut-associated lymphoid tissues as a site of repertoire diversification in swine has been a subject of debate in the literature. Despite the characteristics of a primary lymphoid organ, no direct evidence is available that the swine use the IPP as the site of repertoire diversification. On the contrary, it has been shown that the porcine IPP behaves in a manner distinct from the IPP of sheep and cattle during the fetal B cell lymphogenesis [23]. Furthermore, it is suggested to be a secondary lymphoid tissue [8] that is a part of the mucosal immune system [22, 69]. This demonstrates that neither phylogeny nor anatomical homology is a reliable predictor of repertoire diversification in higher vertebrates.

Like other immunoglobulin classes, IgA consists of two heavy (H) and two light (L) chains, but for IgA, this H₂L₂ monomeric unit can polymerise further. In dimeric IgA, two monomer units are arranged in an end-to-end configuration stabilised by disulphide bridges and incorporation of the J (joining) chain, a 15 kDa polypeptide. Polymerisation is regulated by incorporation of the J chain since its presence stimulates polymerisation [42] and is directed by the COOH-terminal domains of the heavy chains [13]. The J chain is synthesised along with IgA in plasma cells and its incorporation is an early event in IgA polymerisation. Consequently, this peptide is found in all polymeric forms of IgA [96, 99]. Polymerisation of two or more IgA molecules with the J chain occurs late in the secretory pathway, just before release from plasma cells [61].

Mucosal IgA consists predominantly of dimers and some larger polymers (trimers and tetramers), collectively called pIgA [15], and is the major source of IgA present in the serum of most animals including pigs and dogs [64]. In contrast, serum IgA of primates, including humans, is chiefly mono-

meric (mIgA) and is the result of synthesis in the bone marrow [64].

3. TRANSPORT OF pIgA INTO THE MUCOSAL SECRETIONS BY THE pIgR

The central role of pIgA in protecting the mucosal surface relies on the existence of an active mechanism used to transport pIgA across the epithelial barrier into mucosal secretions. The translocation mechanism depends on the interaction with a 110-kDa transmembrane glycoprotein expressed on the basolateral surface of mucosal epithelial cells, termed the pIgR. The pIgR is internalised by endocytosis from the basolateral membrane into basolateral endosomes and subsequently sorted for transcytosis across the epithelial cell [4]. At the apical membrane, the receptor is cleaved by a cell-surface associated serine protease at the junction between the extracellular domain and the membrane-spanning region, after which the extracellular part of the receptor, termed the secretory component (SC), is released into secretions [15, 71]. Consequently, SC is an integral part of the pIgA molecule released into the secretions and is referred to as SIgA. The SC stabilises SIgA by making it more resistant to proteases [26] and through its glycosylated residues, it improves the protective capacity of SIgA by anchoring the antibody within the mucus [81]. Since pIgR transport occurs continuously and independently of binding of pIgA, free SC is released when unoccupied receptors are cleaved. This free SC exhibits scavenger properties with respect to enteric pathogens [80].

The extracellular part of the pIgR contains 5 Ig-like domains (D1 to D5). In humans, the binding of pIgA is initiated by non-covalent interaction at D1, further non-covalent interactions with D2 and/or D3 allow stable binding, after which this complex is stabilised by covalent interactions with D5 by means of disulfide bonds [72]. Both the J chain [42] and the COOH-terminal

domain of the heavy chains [13] are essential for binding of pIgA to the pIgR.

The signals controlling basolateral targeting, endocytosis and sorting of the pIgR for transcytosis in basolateral endosomes involve tyrosine-containing tight beta turns and phosphorylation sites in the receptor's cytoplasmic tail [4, 39].

For most species pIgR has been cloned. The pig pIgR has been cloned from a porcine small intestine cDNA library [104] and from mammary epithelial cells present in pig colostrum [51]. The cDNA sequence shows a high similarity to the pIgR of other species [51]. Alignment of the rat, mouse, human, rabbit and cattle predicted amino acid sequences demonstrated that pIgR is highly conserved both in amino acid sequence and structural organisation [82, 103]. Subsequent alignment of the cytoplasmic tail of pIgR from cattle, men, rabbits, and rats reveals highly conserved areas that may reflect the importance of these regions for intracellular sorting of the receptor [5, 50, 103].

It has been shown that the liver is involved in the SIgA system of the intestine as in addition to pIgR-mediated transepithelial transport, SIgA can be delivered into the intestinal lumen through secretion into bile. However, the amount of pIgA transported and the mechanisms involved vary widely among species [17]. In some animals (rats, mice, rabbits, chickens) large amounts of pIgA are efficiently cleared from the plasma by the liver and transported into bile by a receptor-mediated vesicular pathway across hepatocytes, which synthesise pIgR [17, 18]. On the contrary in humans, dogs, pigs, guinea pigs and sheep, biliary epithelial cells, not hepatocytes, express pIgR and perform the transcytosis and secretion of pIgA into bile [17, 18, 27, 28]. In these species, there is much less hepatic transport of circulating pIgA and much of the SIgA that reaches bile is synthesised locally by plasma cells that populate the biliary tree [17, 18]. This transport of locally produced pIgA is analogous to the

release of SIgA on the surface of various mucosae in the body. The major biological functions ascribed to the secretion of SIgA into bile are the enhancement of immunological defence of the biliary and upper intestinal tracts and the clearance of harmful antigens from the circulation as pIgA-antigen complexes [18].

Although SIgA is the predominant Ig in the majority of mucosal secretions in most mammals, the proportion of SIgA in colostrum and milk varies between species, reflecting the development of differing modes of antibody transfer from mother to offspring. In primates and rodents, IgG is transferred selectively across the placenta (involvement of the neonatal Fc receptor (FcRn) has been suggested [33]), and the chief Ig in colostrum is SIgA. The serum antibody of the newborn is supplemented further in rodents with IgG derived from the colostrum (FcRn is involved in transfer of IgG across the rodent yolk sac, despite the absence of yolk sac cell surface expression of FcRn [25, 33]) that is actively transported across the neonatal gut by FcRn. In contrast, in pigs no transplacental transfer of IgG takes place [23]. Instead, IgG, derived from maternal serum, is the major immunoglobulin class in colostrum and is absorbed across the neonatal gut in a brief time period prior to closure at around 12 to 24 h after birth [41, 90]. In porcine colostrum, the SIgA content is low, whereas it becomes the major antibody in milk [90]. During lactation, pIgA is secreted by mammary gland recruited plasma cells after which they are excreted in milk via pIgR transport [91]. These pIgA exhibit specificity for the antigens present in the maternal digestive tract, the so-called entero-mammary link, which is due to the migration of lymphocytes from the gut to the mammary gland [91].

More recently, porcine FcRn was cloned [92, 106] and its presence was detected by RT-PCR in the porcine mammary gland three days prepartum and on the day of farrowing [92]. This result further supports the theory that in these animals, like in mice,

FcRn is involved in mammary gland IgG transport during collostrogenesis and milk production [25, 33]. However, in the lactating mammary gland FcRn acts primarily as a recycling IgG receptor in a mode that appears to be similar to that proposed for FcRn trafficking during the maintenance of constant serum IgG levels, i.e. FcRn binds and returns its ligands to the vascular space [25]. In addition to FcRn-mediated transcytosis, other pathways are involved in IgG transport into milk [25].

Transplacental transfer of maternal IgG occurs in dogs during the last third of pregnancy [48, 97]. The majority of IgG (90–95%) transfer occurs from the colostrum across the neonatal gut, particularly during the first 12 h [24]. The importance of colostrum as a source of IgG is reflected in the predominance of this immunoglobulin in canine colostrum [37, 84]. The concentration of IgG in colostrum declines over the three days following birth after which SIgA is the major immunoglobulin class [37].

4. GENERATION OF SECRETORY IgA

IgA represents the main element of the humoral immune response which provides protection against pathogens at mucosal surfaces. The predominance of IgA at mucosal sites reflects a combination of a high rate IgA isotype switching among precursor cells in mucosal inductive sites, their selective homing to mucosal effector tissues and their vigorous proliferation after extravasation and differentiation towards IgA-producing plasma cells.

Of all mucosal sites, the IgA⁺B cell development is best studied in the gut. The major inductive sites of gut-associated lymphoid tissues are PP and mesenteric lymph nodes (MLN). The PP are specialised for the induction of antigen-specific IgA lymphoblasts. Within the PP, the specialised germinal centre (GC) microenvironment (TGF- β , IL-10) and the presence of follicular den-

dritic cells (DC) and CD4⁺T cells promote specific class-switching to IgA [15]. The IgA⁺B cells home from PP to the draining MLN and, via the thoracic duct lymph and blood, to the lamina propria (LP) of the gut. However, there is a major difference in lymphocyte circulation in the pig compared with other species. Whereas in other species, the lymphocytes exit the lymph nodes via the efferent lymphatics, the porcine efferent lymph contains very few lymphocytes. Instead, the lymphocytes in the lymph nodes directly re-enter the circulation via the high endothelial venules (HEV) [75]. The preferential homing of IgA⁺ B cells to the mucosal tissues implies the existence of special adhesion molecules as well as factors derived from local environments that selectively attract the circulating precursors of mucosal IgA⁺ plasma cells. The key-receptor ligand pair involved is α 4 β 7 integrin, expressed by lymphocytes, and MADCAM1 (mucosal vascular addressin cell adhesion molecule 1), expressed by LP high endothelial venules [7]. A functional lymphotoxin β receptor (LT β R) on LP stromal cells is further absolutely necessary for the presence of B cells in the LP [46, 70]. Impaired LT β R signalling might result in a decreased local concentration of adhesion molecules and chemokines, causing absence of B cells [29]. However, the molecular mechanisms by which LT-LT β R interactions selectively affect B cell homing to the gut LP remain unresolved. The preferential homing of circulating precursors of IgA⁺, but not IgM⁺ or IgG⁺ plasma cells to the gut LP is explained by the selective response of IgA⁺B cells to CCL25, also known as the thymus expressed chemokine (TECK), a chemokine expressed by the small intestinal epithelium [12]. The ability of IgA⁺ cells to migrate to mucosal tissues other than the gut appears to be due to their responsiveness to CCL28, also called mucosal-associated epithelial chemokine MEC, a CCR10 ligand that selectively attracts IgA⁺ but not IgM⁺ or IgG⁺ plasma cell precursors [53].

Terminal differentiation of the IgA⁺ plasma cell precursors occurs in the effector

sites, especially the LP which is the major site of IgA production. This terminal differentiation is driven by factors in the mucosal environment, including cytokines, especially IL-6 and IL-5 [15].

Peritoneal cavity B1 cells also generate large amounts of gut pIgA [49]. Unlike the pIgA generated in the PP, pIgA production by these cells appears to be independent of T-cell help and GC, and B1-cell derived pIgA are important for preventing systemic invasion by intestinal bacteria [57]. However, evidence of gut pIgA production by B1 cells in species other than mice is not available.

In addition to the PP, other organised lymphoid tissues have been described. Isolated lymphoid follicles (ILF) in the mucosa and submucosal lymphocyte aggregations have been described in humans, mice, rats, rabbits and guinea pigs and are lymphoid tissues representing solitary PP follicles, which play a role in the production of antigen-specific intestinal IgA [35, 54, 62, 65, 77]. Aggregations of 1 000 lymphocytes in the LP crypt of the small and the large intestine of mice, the cryptopatches (CP), were first described by Kanamori et al. [45]. Although these sites are widely accepted as primary lymphoid organs where intraepithelial T lymphocytes expressing the CD8 α homodimer develop de novo from bone-marrow-derived precursors [73, 88], the origin and differentiation of IEL are still a matter of debate [34, 77]. In contrast to mice, cryptopatches could not be found in humans, rats and porcine small intestines [77]. Moreover, in the mouse, rat and human, specialised intestinal villi, called the lymphocyte-filled villi, have been described [65]. In rodents, they are hypothesised to be extra-thymic sites of primary T-cell differentiation, where luminal antigens may play a role in repertoire expansion and/or selection. In humans, they are not the functional homologues of those in mice and rats, but are probably secondary lymphoid tissues, involved in presenting antigens to memory T cells. Until now, organised lymphoid

structures other than PP have not been described in the pig and dog [76].

5. FUNCTION OF IgA IN SERUM AND MUCOSA

In addition to mucosal secretions, IgA is also found in the serum [74]. Whereas SIgA exerts its function in mucosal secretions as the first line of defence by limiting invasion of pathogens, serum IgA may function as a second line of defence by eliminating pathogens that have breached the mucosal surface [74].

Receptors specific for the Fc region of IgA, Fc α R, are key mediators of IgA effector function, providing a link between antibody-antigen complexes and the cellular effector machinery. However, these receptors function as a second line of antibacterial defence utilising serum IgA rather than secretory IgA [66]. Human Fc α R (termed Fc α RI or CD89) was the first to be cloned and characterised and is the most likely candidate for initiation of inflammatory responses involving IgA. It binds poorly to SIgA but vigorously triggers potent effector functions upon binding to serum IgA [74]. The variety of effector mechanisms triggered by ligation of the Fc α R by IgA-containing immune complexes includes antibody-dependent-cell-mediated cytotoxicity (ADCC), phagocytosis by cells of the myeloid lineage including monocytes, macrophages, neutrophils and eosinophils, respiratory burst activity by polymorphonuclear leukocytes and degranulation of eosinophils and basophils [66, 102]. Furthermore, Fc α RI ligation facilitates antigen presentation on human DC [32]. On the contrary, earlier data suggested a non-inflammatory function of IgA. This is accentuated by the fact that IgA is a poor activator of complement although IgA can trigger, under certain conditions, the alternative complement pathway [40], it cannot bind C1q, therefore it cannot activate the classical pathway [47]. However, the ability of IgA to induce phagocytosis has now

been confirmed by several laboratories [74]. While information on human Fc α R has amassed steadily, the Fc α R systems in other species are not yet fully understood. The search for Fc α R orthologues centred initially on the mouse, but despite efforts, no mouse equivalent has been found to date [74]. However, alternative receptors for IgA have been identified in mice. Indeed, on murine B cells and macrophages, a receptor specific for both IgA and IgM Fc (Fc α/μ) has been characterised [89, 93]. It is only recently that the first true orthologues of human Fc α R have been described in rats [58], cattle [67] and macaques [87]. To date, Fc α R has not been described in pigs or dogs.

In contrast to serum IgA, SIgA is incapable of triggering phagocytosis by either neutrophils *in vitro* or Kupffer cells *in vivo* which is presumably due to (partial) blockage of Fc α RI binding site on IgA (both pIgA and mIgA) by SC [38, 101]. This may be of importance in the maintenance of integrity of mucosal surfaces. Indeed, activation of the complement induces local inflammatory reactions, including the influx of polymorphonuclear leukocytes and the release of substances including cytokines that enhance the permeability of mucosal membranes.

SIgA antibodies contribute to the protection of the mucosal epithelial barrier through a variety of mechanisms. The first mechanism of protection by SIgA is active at the stromal side of the epithelium since SIgA can complex with antigens present locally in the underlying tissue. These immune complexes can either be taken up by phagocytic cells, be absorbed into the vascular system, or be transported across the epithelium into the lumen by the same pIgR-mediated pathway utilised by pIgA [44, 85]. By doing so, antigens that leak through the epithelial barrier can be cleared back into the lumen, and monomeric IgA or IgG antibodies, which themselves are not ligands for the pIgR, can be transported as part of these immune complexes [44]. This

immune elimination role of pIgA might provide an effective means of ridding the mucosal tissues of (excessive) immune complexes. Furthermore, during the pIgR-mediated transport process, specific pIgA can bind to newly synthesised viral proteins inside the epithelial cells, preventing virion assembly and neutralising viral replication [11, 31, 60]. Prevention of virion assembly and budding by pIgA acting intracellularly may potentially forestall cytopathic effects, thus sparing the cell and may be a mechanism of recovery from infection. This preservation of mucous membrane integrity helps maintain the epithelial barrier and retards systemic dissemination of viral antigens. Moreover, using an *in vitro* model of polarised intestinal epithelial cells, an anti-inflammatory mechanism of pIgA-mediated protection against intracellular bacterial components that are involved in the proinflammatory activation of the intestinal epithelial cells has been demonstrated. Specific pIgA colocalises to LPS in the apical recycling endosome compartment, preventing LPS-induced NF- κ B-translocation and subsequent proinflammatory response [30]. Consequently, intracellular neutralisation by pIgA limits the acute local inflammation induced by proinflammatory pathogen-associated molecular patterns such as LPS. Finally, SIgA can interact with antigens at the luminal side after epithelial transcytosis. SIgA antibodies can thereby interfere with the ability of antigens, including viruses, bacteria and bacterial toxins and enzymes, to adhere to and penetrate the mucosa, a phenomenon called "immune exclusion" [14]. Because of the polymeric nature of SIgA, it displays greater avidity than monomeric Ig and can efficiently crosslink target macromolecules and micro-organisms, thereby inhibiting motility and facilitating entrapment in the mucus and clearance by peristalsis [83]. Furthermore, SIgA is a hydrophilic, negatively charged molecule because of the predominance of hydrophilic amino acids in the Fc region of IgA, and abundant glycosylation of both IgA and SC [47]. Consequently, micro-organisms

surrounded by SIgA will be repelled by the mucosal surface. Terminal mannose-containing oligosaccharide side chains, particularly those on human IgA₂ heavy chains, are recognised by mannose-specific lectins present on type 1 fimbriae. Consequently, these carbohydrate-specific interactions represent an important protective anti-adherence function of SIgA against bacteria, regardless of the specificity of the pIgA molecule [63]. In other cases, SIgA can directly block the microbial sites that mediate epithelial attachment, either by binding to specific adhesins or by sterically hindering their interaction with epithelial cells.

6. OTHER ANTIBODIES PRESENT IN THE MUCOSA

Although IgA is the most abundant immunoglobulin in mucosa, the other isotypes (IgM, IgG or IgE) are also locally produced in relatively small amounts (< 10%) but their proportion may increase in inflamed or diseased tissues [56] and in cases of IgA deficiency where mucosal IgM production and secretion partly compensates for the lack of IgA [36]. However, in the pig, IgM is a more important mucosal isotype compared with other species and both IgM and IgA are important in the mucosal lymphoid organs, especially in the young pig. Bianchi et al. [9] have studied the postnatal development of the isotype specific Ig-secreting cell response in various lymphoid organs of specific pathogen free (SPF) pigs between 1 and 40 weeks of age. In these SPF-pigs, the shift from IgM to IgA as the predominant mucosal isotype was first observed in the duodenum and jejunum (12 weeks) and later in the ileum (40 weeks). Since antigen exposure may influence the development of the Ig-secreting cell repertoire, the frequencies of Ig-secreting cells in the mucosal lymphoid organs were compared between SPF-pigs and conventional pigs at the age of 40 weeks. At that age, no differences were found between SPF-pigs and conventional pigs

concerning the amount of IgM and IgA in the intestine [9]. Like IgA, IgM has the ability to polymerise, mainly to pentamers with incorporated J chain and to hexamers without the J chain [96]. As for IgA, only the J chain containing IgM polymers binds the pIgR and is transported across the epithelium. However, the mode of pIgR binding differs between pIgM and pIgA and in some species, most notably the rabbit, the ability of pIgR to bind pentameric IgM has been selectively lost [86]. On the contrary, pIgM and pIgA are bound by human pIgR with similar affinity [68]. However, the external transport of pIgA is normally favoured over pentameric IgM because of its dominant local production and its better access to pIgR by enhanced diffusion through the extracellular matrix and epithelial basement membranes [68].

IgG cannot be transported by pIgR. However, it may provide mucosal protection by paracellular passive transfer [71]. Furthermore, a bidirectional transport mechanism for IgG via FcRn is demonstrated, by which IgG is secreted onto mucosal surfaces and scavenges luminal antigens for recognition by the immune system [105].

It has been demonstrated in mice that, the capillaries in the PP mucosa are non-fenestrated and relatively impermeable to serum antibodies [1], making the PP functionally isolated from blood-borne factors. Whether differences in permeability of capillaries exist between the porcine jejunal and ileal PP has not been investigated. On the contrary, the villous capillaries are highly fenestrated allowing diffusion of serum proteins into the LP. Consequently, serum-derived antibodies can be found in the LP. Like locally produced IgA, serum-derived IgA can be transported into the intestinal lumen via pIgR. In the pig, 22.7–29.5% of IgA in the gut lymph comes from serum, versus 77.3 to 70.5% from local production in the intestine [100]. Conversely, 31% of the total plasma IgA originates from local intestinal synthesis, reaching the blood via mesenteric lymph [100]. The majority of

serum IgA in the dog originates from the plasma cells in the intestinal lamina propria since the daily output of IgA from mesenteric lymph into the circulation is greater than the quantity present in the serum and is sufficient to maintain the circulating pool of IgA [43, 98].

7. CONCLUSION

The function of IgA in immunological responses is not yet completely elucidated. However, from studies in humans and mice, it has become clear that SIgA has more anti-inflammatory properties, whereas serum IgA should be defined as an inflammatory antibody through interactions with Fc α RI on effector immune cells. Very little information is available on the function of IgA in immunological responses in large farm and companion animals. Although there is an obvious general similarity to human and mouse counterparts, differences in structure, antibody repertoire development, pIgR-mediated transport, colostrum IgA content, hepatobiliary transport, and function do exist among species. This diversity justifies the quest of veterinary immunologists to define the IgA system for their species of interest rather than making extrapolations from human and mouse immune systems.

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