

# The distribution of SIgA and IgG antibody-secreting cells in the large intestine of Bactrian camels (*Camelus bactrianus*)

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**Background:** Mucosal immunoglobulin comprises mainly secretory immunoglobulin A (SIgA) which mainly participates in the intestinal mucosal pathogen-specific immune response. Immunoglobulin G (IgG) is another common immunoglobulin. Bactrian camels' gastrointestinal mucosal tissue has a special mucosal immune system. However, the distribution characteristics of these two antibody-secreting cells (ASCs) in Bactrian camel's large intestine mucosal immunity system remain largely unknown. This study was aimed to describe the distribution characteristics and density of SIgA and IgG ASCs in the mucosal immunity tissues of Bactrian camel large intestine.

**Materials and methods:** Tissue samples were collected from different parts of the large intestines of 10 healthy adult Chinese Alashan Bactrian camels. Immunohistochemistry technology was used to determine the distribution of SIgA and IgG ASCs in the large intestine samples and the image-Pro Plus 6.0 was employed to calculate their densities.

**Results:** SIgA and IgG ASCs were distributed in lamina propria of the large intestine mucosa with some ASCs aggregating around the intestinal glands. The SIgA density increased from ileocecal orifice to the caecum and decreased from the colon to the rectum. The largest number of SIgA ASCs was observed in the caecum, followed by anterior colonic segments, ileocecal orifice, posterior colonic segments, and rectum, and the number of SIgA ASCs in the caecum was significantly larger than that in other four positions ( $p < 0.05$ ). Similarly, the number of IgG ASCs was also the largest in the caecum, which was significantly higher than that in ileocecal orifice, anterior, posterior colonic segments, and rectum ( $p < 0.05$ ).

**Conclusions:** Our findings suggest that SIgA and IgG ASCs are mainly distributed in intestinal mucosal immunity effector sites. These distribution characteristics provide evidence to support that SIgA and IgG supply effective protection and maintain homeostasis in the large intestinal mucosa. (Folia Morphol 2022; 81, 4: 963–970)

**Key words:** Bactrian camel, large intestine, SIgA, IgG, antibody-secreting cells

## INTRODUCTION

Bactrian camels are ruminants inhabiting desert or semi desert regions, particularly in China. Due to their special feeding habit, Bactrian camels' gastrointestinal mucosal tissue has a special mucosal immune system [5]. For example, the abomasum, one of Bactrian camels' two stomachs, possesses a unique mucosa-associated lymphoid tissue structure [25]. Importantly, the cystic Peyer's patches (PPs) on the surface of the large intestine mucosa are unique to Bactrian camels, and are located mainly on the mucosal surface of the whole ileocecal orifice, the initial segment of the caecum, and the one third segment of the colon. However, there are no PPs on the surface of the rectum. Moreover, the Bactrian camel's ileocecal orifice is the main site of immune induction of the large intestine mucosa. Meanwhile, the PPs gradually degenerate with the age of the camel [31]. Previous studies have shown that the number of lymphatic follicles at the ileocecal orifice of Bactrian camel is the largest (37.7/10 mm<sup>2</sup>), and there are only a small number of lymphoid tissues in the posterior colon and in the rectum. These findings are different from those in human. In the ascending colon of human large intestine, the isolated lymphoid follicle density was 0.02 per mm of muscularis mucosae, but in the rectosigmoid it was increased to 0.06 per mm [19, 31].

The gastrointestinal tract contained a viscoelastic mucus gel layer with a characteristic interaction between the mucin protein network and a large number of antibodies (Ab) [4, 9, 27]. The immune system secretes antigen-specific antibodies, including immunoglobulin G (IgG) and secretory immunoglobulin A (SIgA), which further strengthens this physical barrier [29, 30]. Among all the antibodies secreted by immune system, IgA has been reported to have the largest production [15]. IgA has multiple polymerisation forms with its monomer called mIgA and its external secretory form known as SIgA [17, 18, 22]. IgA enhances immune exclusion by inducing food antigens and microorganisms in mucus and downregulating proinflammatory factor expression in symbiotic bacteria, thus maintaining appropriate bacterial colonies in certain intestinal segments [7, 20, 27, 32]. In addition, SIgA blocks the contact between microorganisms and the epithelium and regulate the neutralisation between pathogens entering the epithelium and their products, thereby promoting the uptake of antigens by M cells [2, 8, 12, 16, 21].

IgG is another important antibody in humoral immunity, and IgG participates in the mucosal immune response via transepithelial barrier transport [28]. IgG subclasses include IgG1, IgG2, and IgG3, accounting for 75% of the total antibodies in circulation, and IgG subclasses of camel family (Bactrian camel, one-humped camel, and American camel) naturally lack light chains and the CH1 region [6, 11, 24, 26, 31].

The proportion of immune cells (antibody-secreting cells [ASCs]) is different in different mucosal regions. For example, SIgA and IgG ASCs account for 79% and 3% in the intestinal mucosa of normal adult human, respectively, whereas their proportion is 69% and 17% in the nasal mucosa and 76% and 13% in the stomach, respectively [2, 29]. However, few reports on the distribution of SIgA and IgG ASCs in the Bactrian camel large intestine are available.

Considering this, the present study was aimed to investigate the distribution of SIgA and IgG ASCs in the Bactrian camel large intestine. The results of this study will provide a theoretical basis for the further research of the immune mechanism in the large intestine of Bactrian camel, and provide reference for the prevention from Bactrian camel disease and the development of vaccine.

## MATERIALS AND METHODS

### Experimental animals

The animal experiments were approved by the Animal Ethical and Welfare Committee of College Veterinary Medicine of Gansu Agricultural University (Approval No: GSAU-AEW-2020-0010). The large intestine samples of 10 healthy Alashan Bactrian camels (5 male and 5 female, 6–8 years old) were obtained from the Minqin Abattoir in Gansu Province, China. All the camels were not starved prior to sacrifice, and they were euthanized using 20 mg/kg sodium pentobarbital and exsanguination until death. The experiments were conducted in the Veterinary Pathology Laboratory of College of Veterinary Medicine, Gansu Agricultural University.

### Microsection preparation

The abdominal cavity was opened and the large intestines were isolated. The ileocecal orifice, caecum, colon, and rectum were sampled for histological analyses. The samples were fixed in neutral paraformaldehyde solution (4%) for more than 15 days. Routine methods were used to obtain paraffin sections, which were subjected to streptavidin-biotin

complex (SABC) staining. The following antibodies were used for SABC staining. Primary antibodies included rabbit polyclonal antibodies for recognising Bactrian camel SIgA (1:400 working concentration) and rabbit polyclonal antibodies for recognising Bactrian camel IgG (1:1200 working concentration). Both primary antibodies were produced in our laboratory (Veterinary Pathology Laboratory of College of Veterinary Medicine, Gansu Agricultural University, China). The second antibody was contained in a SABC goat anti-rabbit polyclonal immunohistochemical kit (Lot No. 07H3OCJ, Boster, Wuhan, Hubei, China). SABC staining was carried out following the manufacturers' instructions.

#### Observation of ASC distribution under light microscopy

Light microscopy was used to observe the local characteristics and distribution of SIgA and IgG ASCs in various parts of the large intestine. For each sample, 30 sections were observed and photographed under an Olympus DP-71 microscopy system (Olympus, Tokyo, Japan).

#### Morphometric and statistical analysis

From each large intestinal segment, five sections were selected randomly. Within each section, 10 microscopic fields were selected randomly, observed, and photographed. We then counted the number of SIgA and IgG ASCs in each microscopic field and calculated their respective densities by using Image-Pro Plus 6.0 (Media Cybernetics, Rockville, MD, USA). The one-way ANOVA with Duncan's multiple range test was performed to determine the statistically significant differences in the distribution densities in all large intestinal segment sites between the SIgA and IgG ASCs. Statistical analyses were performed using IBM SPSS V.17.0 (IBM Corp, Armonk, NY, USA) and graphs were drawn using Originpro 2018 (OriginLab Corporation, Northampton, MA, USA).  $P < 0.05$  was considered as statistically significant.

## RESULTS

#### SIgA and IgG ASCs distributions in Bactrian camels' large intestines

The distribution of SIgA ASCs was similar in the ileocecal orifice, caecum, colon, and rectum. Some SIgA ASCs were scattered in the lamina propria (LP), and some SIgA ASCs aggregated around the intestinal glands (Fig. 1). However, their distribution was

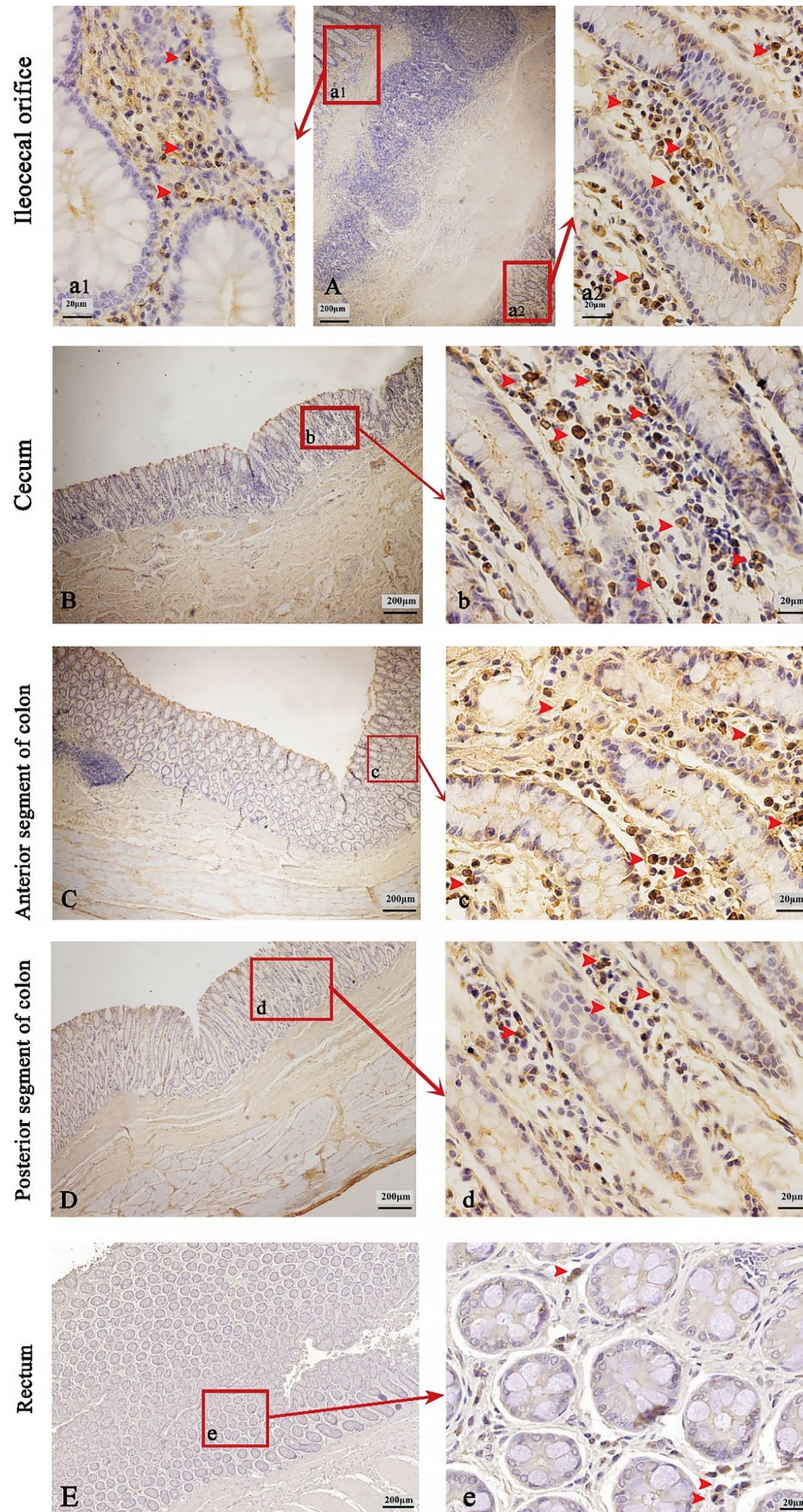
sporadic in the area of lymph nodules and the domes of diffuse lymphoid tissue. In the same regions, the distribution IgG ASCs and SIgA ASCs were distributed similarly. IgG ASCs also appeared scattered in the LP with most of them aggregating around the intestinal glands (Fig. 2). This distribution characteristics might provide effective protection for the large intestine mucosa of Bactrian camel.

#### SIgA and IgG ASC densities in large intestines of Bactrian camels

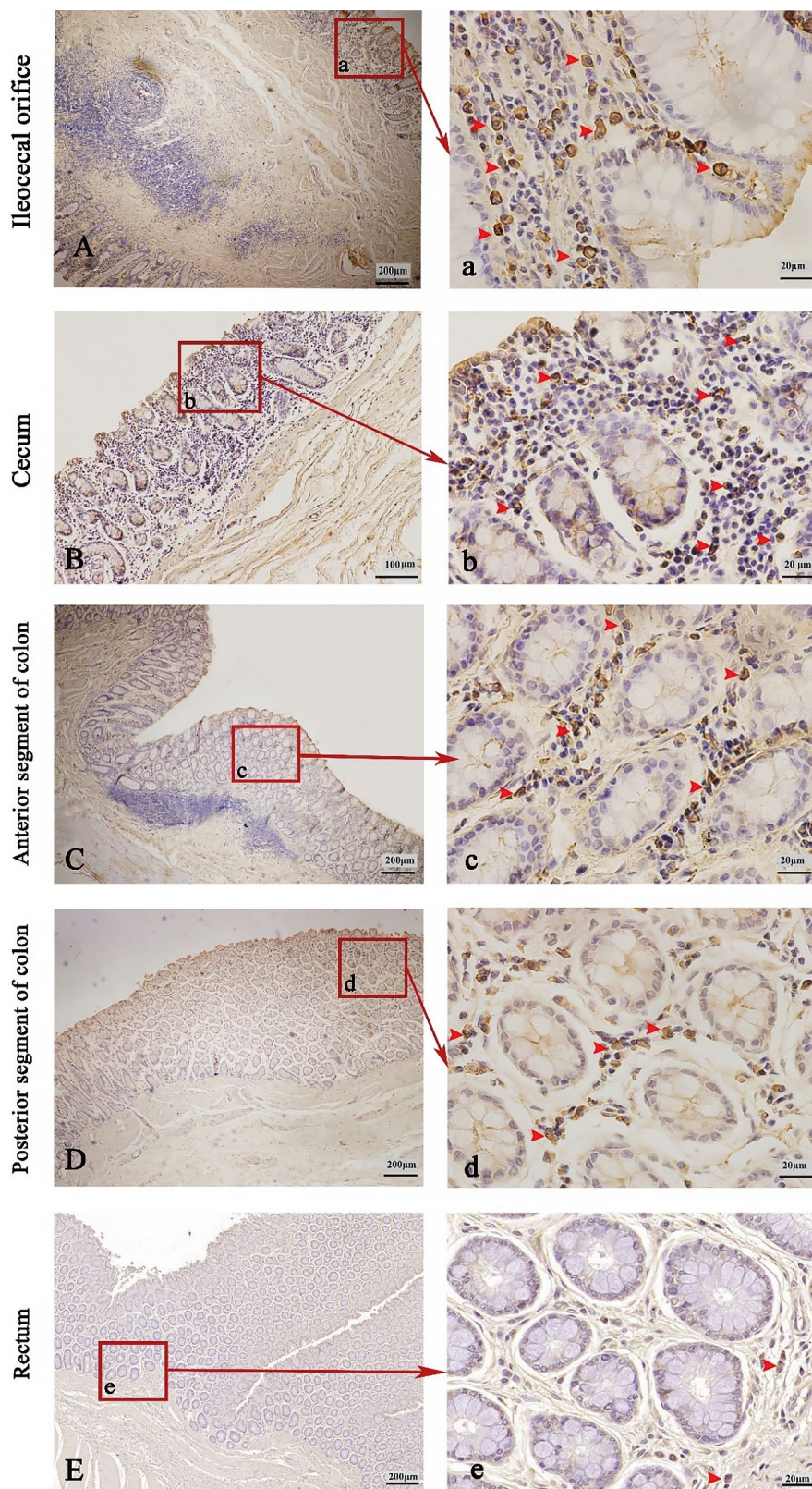
Our data showed that the density of SIgA increased from the ileocecal orifice to the caecum and decreased from the colon to the rectum. In the same region, the distribution density of SIgA ASCs was higher than that of the IgG ASCs (Figs. 3, 4). SIgA ASCs showed the highest density in the caecum ( $11.33 \pm 1.06$ ) and the lowest one in the rectum ( $3.21 \pm 0.83$ ). Their density was significantly higher in the caecum ( $11.33 \pm 1.06$ ) and anterior colonic segments ( $10.14 \pm 1.90$ ) than in the ileocecal orifice ( $8.10 \pm 1.11$ ), posterior colon ( $6.64 \pm 0.99$ ), and rectum ( $3.21 \pm 0.83$ ;  $p < 0.05$ ; Table 1). IgG ASC density was also the highest in the caecum ( $10.61 \pm 2.10$ ), but it was lowest in the rectum ( $2.87 \pm 0.79$ ). IgG ASC density was significantly higher in the caecum ( $10.61 \pm 2.10$ ) than in ileocecal orifice ( $6.06 \pm 1.52$ ), anterior colonic segments ( $6.07 \pm 1.53$ ), posterior colonic segments ( $6.33 \pm 0.90$ ), and rectum ( $2.87 \pm 0.79$ ;  $p < 0.05$ ; Table 1). These statistical results showed that the caecum is the main effector site of large intestine mucosal immunity in Bactrian camel.

## DISCUSSION

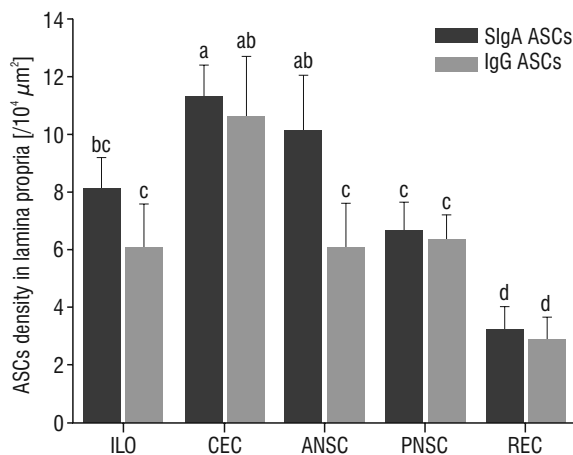
The mucosal immune system of digestive tract is mainly composed of two parts, namely, mucosal immune induction region and effector region. Our data showed that SIgA and IgG ASCs were distributed among the Bactrian camel large intestinal LP, and most of them were aggregated around the intestinal gland, and these distribution regions were the effector regions of mucosal immunity in Bactrian camel large intestine. Our results indicated that immune system might have shortened the distance which ASCs travelled to deliver immunoglobulins to effector sites so as to remove invaders in a very short time, thus further increasing accuracy and sensitivity of immunosurveillance and immune exclusion. In mucosal immunity system, SIgA can act as the protective layer in the lumen through the transcytosis of pIgR [3].



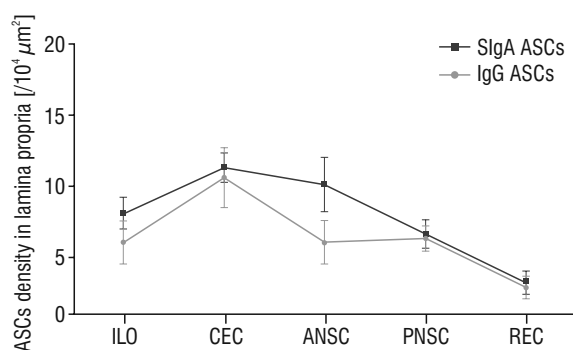
**Figure 1.** Immunohistochemical staining of SIgA antibody-secreting cells (ASCs) in the ileocecal orifice, caecum, anterior, posterior segments of the colon, rectum of Bactrian camel; **A.** Distribution of SIgA ASCs in the ileocecal orifice lamina propria (LP); **B.** Distribution of SIgA ASCs in the caecum LP; **C.** Distribution of SIgA ASCs in the anterior segments of the colon LP; **D.** Distribution of SIgA ASCs in the posterior segments of the colon LP; **E.** Distribution of SIgA ASCs in the rectum LP. SIgA ASCs were scattered in the large intestinal LP, and some of them aggregated around the crypts. Red triangles indicate SIgA ASCs. The red square pictures (a–e) represent the four sublocations. The original magnification of the images in A–E pictures is  $\times 40$ , and that of images a–e is  $\times 400$ .



**Figure 2.** Immunohistochemical staining of IgG antibody-secreting cells (ASCs) in the ileocecal orifice, caecum, anterior, posterior segments of the colon, rectum of Bactrian camel; **A.** Distribution of IgG ASCs in the ileocecal orifice lamina propria (LP); **B.** Distribution of IgG ASCs in the caecum LP; **C.** Distribution of IgG ASCs in the anterior segments of the colon LP; **D.** Distribution of IgG ASCs in the posterior segments of the colon LP; **E.** Distribution of IgG ASCs in the rectum LP. IgG ASCs were scattered in the large intestinal LP, and some of them aggregated around the crypts. Red triangles indicate IgG ASCs. The red square pictures (a–e) represent the four sublocations. The original magnification of the images in A–E pictures is  $\times 40$ , and that of images a–e is  $\times 400$ .



**Figure 3.** Bar graph of the density of SIgA and IgG antibody-secreting cells (ASCs). The density of SIgA and IgG ASCs in each segment of Bactrian camel large intestine (unit: /10<sup>4</sup> μm<sup>2</sup>); ILO — ileocecal orifice; CEC — caecum; ANSC — anterior segments of colon; PNSC — posterior segments of colon; REC — rectum.



**Figure 4.** Line chart of the density of SIgA and IgG antibody-secreting cells (ASCs); ILO — ileocecal orifice; CEC — caecum; ANSC — anterior segments of colon; PNSC — posterior segments of colon; REC — rectum.

Meanwhile, FcRn is an IgG receptor, and it can be combined and released in both directions between lumen and mucosa [1]. The distribution characteristics of SIgA and IgG ASCs suggest that they play an important role in forming the antibody protective barrier in intestinal mucosal immunity system. However, once

the protective immunoglobulin barrier is damaged, the intestine will become increasingly vulnerable to intestinal pathogens.

In addition, our data showed that the distribution pattern of SIgA and IgG ASC densities consistently increased from the ileocecal orifice to the caecum, and then decreased from the colon to rectum. The SIgA and IgG ASC densities were highest in the caecum. Based on these results, we speculated that the caecum of Bactrian camel might be the main effector site in mucosal immunity. It might be related to the function of the digestive system of ruminants. For ruminants, the contraction of their ileocecal sphincter can prevent the chyme reflux in the ileum; when chyme moves through the large intestine, its retention time increases in the ileocecal orifice; the bulk of the chyme enters the colon, and some of it returns to the caecum through antiperistalsis of the colon [5, 31], which support our results that SIgA and IgG ASC densities were highest in the caecum. This might explain why maintaining an appropriate level of antibody protection in the caecum region is conducive to capturing antigens by the host, thus inducing mucosal immune response and immune monitoring. Our results indicated that in the same region, the distribution density of SIgA ASCs was higher than that of IgG ASC, which is in line with the previous observation in the intestines of humans, rats, and mice [2]. When pathogenic bacteria invade, a large number of SIgAs are secreted and transported to form a first-line immune barrier, thus regulating immunity and maintaining intestinal microecological homeostasis [15, 22]. If pathogenic bacteria destroy the first-line immune barrier and go through the epithelial layer, IgG will quickly recruit innate immune cells to form second line of defence so as to remove pathogenic bacteria [14]. Therefore, the distribution density of these two types of ASCs provide evidence that SIgA and IgG can form two lines of immune barriers in the large intestine of Bactrian camel. The distribution pattern revealed in this study might be associated with the Bactrian camel's gut microbiota and mucosal immunity.

**Table 1.** The distribution density of secretory immunoglobulin A (SIgA) antibody-secreting cells (ASCs) and immunoglobulin G (IgG) ASCs in the large intestine of Bactrian camels (x ± SEM) unit: /10<sup>4</sup> μm<sup>2</sup>

	Ileocecal orifice	Caecum	Anterior colonic segment	Posterior colonic segment	Rectum
SIgA ASCs	8.10 ± 1.11 <sup>bc</sup>	11.33 ± 1.06 <sup>a</sup>	10.14 ± 1.90 <sup>ab</sup>	6.64 ± 0.99 <sup>c</sup>	3.21 ± 0.83 <sup>d</sup>
IgG ASCs	6.06 ± 1.52 <sup>c</sup>	10.61 ± 2.10 <sup>ab</sup>	6.07 ± 1.53 <sup>c</sup>	6.33 ± 0.90 <sup>c</sup>	2.87 ± 0.79 <sup>d</sup>

Data in a row marked with different superscripted letter (a, b, c, d) differ significantly (p < 0.05).

Complex microbial communities play an important role in the host immune system [10]. The intestinal microbiota and their metabolites not only provide the nutrition required by the host, but also compete with invading pathogens for the same colonisation niche, thereby exerting a vital function in the regulating host adaptability [23]. Colonisation of microbial communities at mucosal immune induction sites stimulates the host to initiate a series of mucosal immune responses. Symbiotic microbiota play an important role in mucosal immunity. For example, segmented filamentous bacteria can stimulate the development of Peyer's patches (PPs) and promote the production of IgA [13]. The abomasal lymph node area (ALNA), ileum PPs, and caecum PPs in Bactrian camel constitute the immune induction site of digestive tract mucosa. Colonisation of bacteria on different immune induction sites may stimulate different immune responses, which results from mutual selection and adaptation. Previous 16S rDNA-Illumina Miseq sequencing analysis has indicated that the microbiota characteristics are very different between ALNA and ileum PPs in Bactrian camel [8]. PPs in the caecum of Bactrian camel were a special type of cystic PPs, which may increase the contact area with pathogens. This special cystic structure of PPs may also be related to the diversity of parasitic bacterial community, and it can stimulate different immune responses [31].

Microbial diversity and intestinal microbial metabolomics related to mucosal immunity remain to be further explored. Our results will lay a foundation for further study of Bactrian camel large intestine microbial colonisation and mucosal immune pathways.

## CONCLUSIONS

Our results show that SIgA and IgG ASCs are mainly distributed in LP of ileocecal orifice, caecum, colon, and rectum of Bactrian camels. Their distribution density increases gradually from the ileocecal orifice to the caecum and then decreases progressively in the rectum, and the density of both SIgA and IgG ASCs is the largest in the caecum. Thus, in the Bactrian camel, mucosal immunity is likely to be affected by the caecum of the large intestine.

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**Conflict of interest:** None declared

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