

Immunological Responses in Camelids: A Comparative Study of Mammary Gland Health and Disease

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Abstract

Dromedary camel (*Camelus dromedarius*) can survive and produce considerable amount of milk during recurrent and prolonged hot and dry environment. Camel milk considered one of the most valuable food sources due to its nutritional value. Intramammary infection and other low hygienic measurers are the main factors that undermined the camel mammary gland welfare. Available studies elaborated in detail the role of innate factors like Peptidoglycan recognition protein and Lactoferrin in camel milk as potent antimicrobial factors. Despite the wide studies on camel antibodies, their role in the mammary gland immunity was scarcely addressed. The major lack of information about the immune system of camel mammary gland is of great setback in improving the camel dairy industry. This review has evaluated the available data on different aspects of the mammary immune system. The available data unfortunately are of general profile, which created wide gaps in understanding the camel mammary gland immune system in health and disease. Several measures were proposed as necessary approaches to drive considerable interests of wide and in depth research on the camel mammary gland immune system.

In conclusion, the available knowledge on the immune system of camel mammary gland suffers from major lack in the role of the immunoglobulins in health and mastitis. Although, acceptable progress was made on defining the cellular populations of the mammary gland, their main activity during the infection needs to be revealed.

Keywords: LPAM-1; Majahiem; Nano antibodies; Milk; Saudi Arabia; Mastitis; Lactoperoxidase

Introduction

Population and breeds

In Saudi Arabia, the camels' population in 2010 was estimated 850,000 heads of different breeds [1]. However, the camel population was estimated in 2015 as 3,113,628 heads in which, females were the highest 1,133,988 and males were only 222,741. The Eastern province was the highest in the females' population, 223,182 heads, whereas Makkah Al Mukarramah was the highest in males' population, 44,919 heads [2].

The indigenous camels in Saudi Arabia are traditionally classified into four different breeds; they are Maghatier, Shu'l, Majahiem and Soffer, in which Majahiem is considered more appropriate for milk production [1,3]. Other breeds with well-developed udder are also recorded but with limited geographical distribution, they are Homor, Shaele, Sofor and Waddah (Maghatir) [4].

Camel breeds indicated wide differences in the physical properties. In regard to the size of the body and the color of the coat, Homor is medium size with clear brown coat, while the Majaheem has black coat with long legs and well-developed udder. The Saheli breed, which more restricted to the Red sea area, has red coat color with small udder. The Sofor on the other hand, is characterized with dark brown coat and well-developed udder despite its high resistance to the harsh desert weather. Finally, Waddah or (Maghatir) has well-developed hump and the coat color is white [4].

A considerable variation in the milk constituents of well-known camel dairy breeds were recorded [1]. The protein, lactose, solid none fat and fat composition of Sofor milk were the highest of all of the breeds. The K^{++} and Ca^{++} contents of the Maghatier milk were the highest in comparison to its counterparts [1].

The anatomy of the camel MG

Similar to cow, the camel mammary gland (MG) is consisted of four glandular quarters and it is located in the inguinal region. The left and right halves of the udder are separated from each other by fibroblastic tissue extending from the linea alba and pre pubic tendon. A groove is generally visible between the left and right half, which is more distinct in the lactating than in the dry period. The lateral aspect of the quarters is covered by tissue from the abdominal tunica and the caudal abdominal wall. Although, the anterior (front) and posterior (back) quarters are independent and totally separated, the separation between them is invisible from the outside [5]. The camel MG however, has no gland cistern i.e., no milk reservoir beyond the teat cistern. Similar to those of the cow, gland cistern consist of compound tubule-alveolar glands, parenchyma, connective tissue stroma, ducts, and alveolar systems, [5]. Schwartz and Dioli (1992) demonstrated that the bovine teats possess only one duct cistern whereas, the teat of the camel possess 2-3 cisterns. Each teat cistern is spindle shape, tapers distally, and possess streak canal. The streak canals are short and small so that ordinary cannula used in the udder of the cow is too large for the camels [6].

The economical and nutritional value of camel milk

Dromedary camel (*Camelus dromedarius*) can survive and produce considerable amount of milk during recurrent and prolonged hot and dry environment [7]. Camel milk and meat are considered important source of proteins for wide range of population [8]. It was estimated that world camel milk market worth 10 billion dollars [8].

Thus, camel milk is considered one of the most valuable food sources due to its nutritional value [9,10]. The daily milk production by the indigenous breeds range from 6-8 liter/head. The total annual production was estimated 2500-4900 liter [11] with the lactation period of 8 to 18 months [9]. The Saudi Arabia considered one of the largest camel milk consumers in the World. It was estimated that the annual consumption of the inhabitant in Saudi Arabia reaches 33 liter/hab [12].

In general, camel milk constituent is similar to that of cow milk [10]. The camel milk contains 81.4-87% water, 10.4% dry matter, 1.2-6.4% milk fat, 2.15-4.90% protein, 1.63-2.76% casein, 0.65-0.80% whey proteins, 2.90-5.80% lactose and 0.60-0.90% ashes. Several factors affect the camel milk constituents mainly are, breed, parity, stage of lactation and production system [1]. The amino acids constituent of the camel milk is similar to cow milk. Glutamic acid is the major amino acid of camel milk, whereas lysine represents the lowest amino acid. The camel milk proteins could be considered as a satisfactory nutritional source for human [10]. The constituent of the major salts of camel milk, Ca, P, Na and K are similar to the cow milk [10]. The major vitamins of the camel milk are niacin and vitamin C. The vitamin B1, B2 and folic acid are of low concentration in the camel milk [10].

The study of milk contents of the three camel breeds in Saudi Arabia, Majaheim, Wadah and Hamra indicated significant differences [13]. The Majaheim milk content indicated the highest level in protein, fat and total solid constituent. Wadah milk content however, was the lowest in the milk content values. The milk pH value of the three breeds registered no significant differences [13].

Mastitis of camel MG

Mastitis is worldwide disease of dairy animals that result in heavy economic losses in milk production [14]. The average prevalence of the camel mastitis in selected pastoral areas in Eastern Ethiopia was estimated 76% [15]. In Saudi Arabia, the incidence of camel subclinical mastitis was estimated 15.8%-54.6% based on breed, parity and stage of lactation. The higher incidence was related to the fourth parity and it was significantly higher in the early stage of lactation and Shu'1 was the most susceptible breed [3].

Streptococcus agalactiae, other *Streptococcus* spp., *Staphylococcus aureus* (*S. aureus*), coagulase-negative staphylococci, and *Escherichia coli* (*E. coli*) were recorded as the major etiological agents of mastitis in camel [15,16].

The medicinal value of camel milk

In addition to its nutritional value, believe is exist that camel milk has the therapeutic potential for several diseases. For instance, in India, camel milk was used for the treatment of jaundice, tuberculosis, asthma, and anemia and as laxative [17]. However, an extensive search in three websites, MEDLINE (1946 to March 2016), EMBASE (1974 to March 2016), and Google Scholar did not reveal solid evidence that camel milk has substantial therapeutic potential [18]. This search results revealed that camel milk treatment of diabetes, autism, cancer, heavy metal toxicity colitis, alcohol-induced toxicity and various infections in animal models and human failed to reveal decisive results [18].

Innate Immunity

The anti-microbial secretions in camel milk

Camel milk is rich with several proteins that are well known of their innate immunity activities, [19]. The most important of these proteins are:

Peptidoglycan recognition protein (PGRP)

The PGRP is pattern recognition receptor (PRR) that plays important role in preventing the adhesion and bacterial multiplication through the attachment to the lipopolysaccharides (LPS) and lipoteichoic acid

(LTA) of Gram-negative and the Gram-positive bacteria, respectively [20]. The PGRP is an important bacterial inhibitory protein that present in high concentration in camel milk and has the MW of 19.11 KD and its cDNA full sequence is 700 bp. The PGRP concentration in camel milk is 370 mg/L and its expression was seen constant during the lactation period [10,19]. The antiinflammatory activity of the camel PGRP was demonstrated in mice model intoxicated with LPS or LTA by inhibition of the proinflammatory cytokines, tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) and the dramatic reduction in the mortality rate [20].

Lactoferrin

The Lactoferrin also called lactotransferrin is a preservative agent in food, drug and cosmetic. Lactoferrin is major protein, that transfer or store iron in bodily secretions like milk and in the phagocytic cells like neutrophils [10]. Lactoferrin is glycoprotein with MW of 75.3-79.5 KDa. The Lactoferrin cDNA is made of 2336 bp and the total amino acids of the Lactoferrin mature protein are of 689 amino acids [10,21]. The Lactoferrin concentration in camel milk is the highest among the ruminant. In the camel milk, Lactoferrin level drops markedly after few weeks' postparturition [10].

The antibacterial and antiviral activities of the Lactoferrin were widely recoded [21-23]. Lactoferrin exerts its effect by depriving pathogen utilization of iron by depletion. The camel milk Lactoferrin was shown to inhibit the *E. coli* and *Salmonella typhimurium* [21]. The antiviral activities of the Lactoferrin were shown to be effective in blocking the viral attachment to the mucosal surfaces and inhibition of the viral multiplication [24]. The Lactoferrin of the camel milk was shown to have inhibitory effect on the hepatitis C virus entry to the human cells and its multiplication [25].

Lactoperoxidase

It is important antibacterial protein that protects the udder from the bacterial infection. The main antibacterial activities are against the Gram-negative bacteria mainly the lactic acid bacteria. The protein is found in tears, milk and saliva. It has high level in milk during all the stages of the lactation period [10,21]. The protein MW is 78 KDa and its cDNA is made of 2636 bp. The protein is highly similar to the Lactoperoxidase of the human and cattle. The Lactoperoxidase antibacterial activity is conducted through the H_2O_2 to catalyze the oxidation of thiocyanate. Thiocyanate is the substrate of the Lactoperoxidase in milk in which its oxidation has lethal effect on the structure of the Gram-negative bacterial cell was. The structural damage of the bacterial cell wall will result in diffusion of the electrolytes, the amino acids and the polypeptides outside bacteria [10,26].

Lysozyme

The enzyme found in milk, tears, nasal secretions and urine. The lysozyme MW is from 14.4-15 KDa and its secretion level in camel milk recorded the highest among the ruminant. The enzyme attacks the peptidoglycan of the bacterial cell wall moiety by disrupting the glycosidic bonds [21].

Lactophorin

Lactophorin (proteose peptone component-3) is a member of the glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) [19]. Lactophorin level in camel milk appears after 48 hours after the lactation begins. The protein was shown to have important role in

preventing mastitis in camel MG and play a role in interfering with the establishment of pathogens in the gastrointestinal and respiratory tract of the young animals [19].

The phagocytes of camel MG

The microscopic and the pathophysiological details of the camel milk cells were not fully exploited. One of the earliest studies on the cellular population of camel milk in lactation and dry period indicated that the macrophages are the predominant cells with few neutrophils and lymphocytes. The macrophages were irregular in shape with diameter 8.8-11 μm . The neutrophils size however was 8.3-10.2 μm and characterized with lobulated nucleus [4].

The camel blood neutrophils ultra and macromolecular structures were studied in details [27]. Using light and transmission electron microscopy, the study revealed novel structure of camel neutrophils. The ultrastructure study indicated that the cell surface has ruffle appearance due to many pseudopods, while the center of the cytoplasm is dense with variable size and forms of granules. The camel neutrophils cytoskeletal machinery is equipped with different organelles like mitochondria, cytoplasmic reticulum and Golgi apparatus. The neutrophils cytoskeletal contents are arranged in such a way that they facilitate the robotic organelle movement, phagocytosis and microbicidal effect. The efficient microbicidal activity of the camel neutrophil is a result of the novel structure of the high euchromatic and multi-lobulated feature of nucleus [27].

Study on the camel CD markers and the adhesion molecules of the camel MG and milk cells in healthy animals revealed a very few details either due to lack of the specific anti-camel CD markers antibodies or their low expression [28,29]. However, study on camel cells from MG with mastitis revealed the significant expression of the chemokine receptor CXCR2 and the adhesion molecules CD11a/CD18 and CD62L [30].

CXCR2 is an important chemokine receptor for CXCL8 (interleukin-8). It also mediates the interaction of the chemokines CXCL2, CXCL3 and CXCL5. These chemokines are mainly responsible for attracting and recruiting neutrophils [31]. The CXCR2 level elevates as a response to the pathogen associated molecular patterns (PAMPs) of different bacteria.

The CD11a/CD18 is usually expressed on T and B-lymphocytes, macrophages, NK cells, and granulocytes [32]. The CD11a/CD18 is a major integrin expressed in response to the pathogens associated molecular patterns (PAMPs) like *S. aureus* or *E. coli* [32].

CD62L is an important selectin that mediates the naive lymphocytes to the peripheral lymph nodes and other mucosal associated lymphoid tissue. The marker is also expressed on mucosal lymphoid sites and spleen. The CD62L expression on the milk neutrophils in cattle MG was detected before parturition, but their level of expression decreased markedly few hours after parturition [33].

The CD62L expression was detected using flow cytometry study on the milk cells of camel with Gram (+) or Gram (-) mastitis. The findings indicated distinct differences in the expression level of CD62L between Gram (+) and Gram (-), which might reflect the differences in the nature of the immune responses through the amount and type of the recruited lymphocytes [30].

Unfortunately, there are few or scarce understanding of the biological activities of the camel milk phagocytes in health and disease. However,

few available data indicated that the CD markers and the adhesion molecules of camel cells have certain role in recruiting and activating the MG cells during the infection [30].

The Complement System

The camel complement system lacks enormous details about the structure of the components and the role of the system in the innate and acquired immunity. Nevertheless, the main factors influencing complement classical and alternative pathways activity were addressed [34,35]. The classical and alternate complement systems showed their significant effect in young ages (1-5 years old) in comparison to the old ages (10-15 years old). The classical but not the alternate system showed significant higher activities in adult male than female [34,35]. Unfortunately, there are no recent studies on the complement system. Hence, this major lack of knowledge has great impact on understanding the camel immune system.

The complement of the cow MG was detected in low concentration [36]. The alternate but not classical pathway was seen active in the MG due to lack of C1q. The complement 5a (C5a) is involved in aggravation of the inflammatory responses. C5a has significant influence on efficient phagocytosis like attraction of neutrophils but the role of the complement in initiation of inflammation is not definite [36].

The Cytokines

The camel (*Camel bactrianus*) cDNA of the Th1 cytokines (interleukin-2 (IL-2) interleukin-12 p35 (IL-12 p35), interferon- γ (IFN γ) and the Th2 cytokines (interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13) were cloned and analyzed [37]. The nucleotide sequence homology of the camel cytokines genes to the other mammalian cytokines, like pigs, horse, human and mouse ranged from 58-100%. The role of cytokines in the immune responses of MG was not addressed. However, the inflammatory cytokines were elevated in camel as result of infection or vaccination. The upregulation of the cytokines IL-6, IFN- γ , IL-10, interleukin-1 α and β (IL-1 α and β) and the TNF- α was detected with real time polymerase chain reaction (PCR) in camel vaccinated with strain 19 of *Brucella abortus* [38]. The increases in the level of the same cytokines were also detected in camel infected with *Mycobacterium avium* subspecies *paratuberculosis* (MAP) [39].

The Acquired Immunity of Camel MG

The structure and function of antibodies

Camel milk has three immunoglobulins (Ig) classes, IgG, IgA and IgM [10,21]. The IgG is made of three subclasses, IgG1, IgG2 and IgG3 in which IgG2 and IgG3 are made of only heavy chain while the IgG1 has the typical IgG structure. The MW of the purified IgG subclasses are, IgG1 50 KDs, IgG2 46 KDs and IgG3 43 KDs [10,21]. The subclasses IgG1 and IgG2 dominate the immunoglobulin content of colostrum with higher level of IgG1 (91.6%) [10,21]. The maternal transfer of IgG1 and the heavy chain antibodies to camel calf was documented within 24 hours of parturition [40]. Unfortunately, the role of the antibacterial IgG subclasses in immune responses to the pathogens involved in mastitis is not clear. However, the heavy chain antibodies were seen highly efficient competitive inhibitor in blocking the active site of certain enzymes [21]. In cow IgG and IgM are the major opsonic antibody classes in mastitis. However, IgM in the adult

cow is the predominant opsonic antibody class. The Ig of cow MG also play major role as antitoxin and neutralizing factors [36].

The cellular immune responses

The trivial body of information about the camel MG cells type and their responses is of great obstacle in drawing distinct picture of the cell-mediated responses. One of the major missing details is the cellular population of T-lymphocytes and their modulation during different stages of lactation. The available information has indicated possible changes in the cellular population during the mid and late lactation [28]. The immunohistochemical study of the camel MG and the related lymph nodes indicated that CD8⁺ was distinctly expressed at mid lactation, while the Work Shop Cluster+1⁺ (WC+1⁺) was highly expressed in the late lactation [28]. The domination of the CD8⁺ Tlymphocytes during the mid-lactation was documented in the bovine MG [41]. It is well known that CD8⁺ cells act as T-cytotoxic cells, however their major function during the mid-lactation is not clear [42]. It was speculated that these cells could act as immunosuppressive cells during the periparturient period [43]. On the other hand, CD8⁺ cells with $\gamma\delta$ T-cell receptor (TCR) are considered potent source of IFN- γ [42]. The expression of WC+1⁺ strongly advocates the prevalence of the $\gamma\delta$ T-cells that express WC+1⁺ coreceptor in the late lactation of the camel MG [28]. Furthermore, the domination of the Th1 CD4⁺ T-lymphocytes in the late-lactation of bovine MG [41] was attributed to the predominance of the $\gamma\delta$ T-cells due to the copious production of IFN- γ and high expression of IL-12 receptor (IL-12R) [44].

The mucosal nature of the cellular trafficking to camel MG

Lymphocytes recirculation is either of peripheral or mucosal nature [45]. Kehrl and Harp (2001) have shown a difference in the lymphocytes recirculation from mucosal and peripheral tissue between the MG of the ruminant and other monogastric animals. It appears that ruminant cell trafficking pathway is not part of the common mucosal immune system as it was defined for the monogastrics.

The important adhesion molecules that drive the lymphocytes trafficking are mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) and the Peyer's patches adhesion molecule-1 (LPAM-1). MAdCAM-1 expression was detected in the healthy MG tissues, while the LPAM-1 was detected on cells of normal and infected camel milk [28-30].

LPAM-1 is an integrin, which is constructed from subunits $\alpha 4$ and $\beta 7$ and expressed on the lymphocytes, monocytes, eosinophils and basophils but not on neutrophils. LPAM-1 is the specific ligand of MAdCAM-1, which promotes the homing of leukocytes to mucosal tissue [46].

This selective expression of MAdCAM-1 in different tissues was seen the prime factors that mediate the specific migration of lymphocytes. For instance, the expressed MAdCAM-1 in mesenteric lymph node or peyer's patches has selective binding with L-selectin due to the specific glycosylation modification [47]. However, the MAdCAM-1 expression on the HEV around the MG lobules mediates the selective binding to LPAM-1 but not L-selectin [47]. However, it was demonstrated that bovine mammary tissues lack distinct expression of MAdCAM-1 due to very low MAdCAM-1 mRNA transcriptional activity [48].

Hence, the significant expression of LPAM-1 by normal milk cells and cells from infected camels and MAdCAM-1 expression in MG tissues and related lymph nodes most probably advocates the notion that

the cell trafficking to the camel MG is of mucosal basis. The possible mucosal origin of the cellular trafficking in camel MG has fundamental impact on the approaches to study mastitis pathogenesis and vaccine application to different mastitis pathogens.

The prospect of the research on the immune system of camel MG

Although, the rhythm of research on the immune system of the camel MG increased dramatically in the last decade, the research failed to establish distinct details of this system. This failure can be exploited partially by a simple survey to indicate the low scale of research in the camel MG immune system and the low numbers of in-depth research in camel MG.

The survey was conducted in form of a search in Google scholars and PubMed to compare the differences in numbers of research on the bovine and camel MG. The search in Google scholars has shown that the total research conducted on camel mastitis so far was 3470 publications while on bovine mastitis were 62800 publications. However the search output in PubMed was 27 and 7684 publications for camel and bovine, respectively. On the other hand, using the keywords "immune responses" and "camel MG" the search output was 3270 publications in Google scholar and 0 publication in PubMed. Replacing the key word "camel MG" with "bovine MG" the search results were 36800 publications in Google scholars and 91 publications in PubMed.

Despite the acceptable level of publications on the camel mastitis and certain aspects of immune responses in camel MG, in depth research on the major issues of immune responses in camel MG in health and disease is daunting. The details of the cellular populations at different stages of lactation, the role of different T-lymphocytes in immune defences and the cooperation level of innate immunity with the tow arms of acquired immunity are decisive in comprehending the immune responses in camel MG. In addition, major lack in defining the phenotypes of CD4⁺ and CD8⁺, and the existence of natural killer (NK) cells, the extent of the involvement of neutrophils, macrophages and dendritic cells in innate and acquired immunity are major obstacles that pave the way for designing effective vaccines and development of efficient welfare program to tackle the economic losses inflicted by mastitis.

Enhancing the research on the camel MG immune system is greatly dependent on certain executive measures. The below suggestions in the authors opinions could have certain influence on enhancing the research on camel MG, like:

- Developing groups of research that share expertise and knowledge.
- Encouraging the Funds that drive the research projects to fill the major gaps in understating the immune responses in camel MG.
- Camel scientific societies and camel research centres in particular and veterinary associations of countries that possess higher camel populations should embark in intensive scientific activities, like specialized conferences, databases, webinars and workshops for the smooth share of knowledge and to propagate the research interest among scientists.

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