



Recent Advances in Camel Immunology

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Camels are domesticated animals that are highly adapted to the extreme desert ecosystem with relatively higher resistance to a wide range of pathogens compared to many other species from the same geographical region. Recently, there has been increased interest in the field of camel immunology. As the progress in the analysis of camel immunoglobulins has previously been covered in many recent reviews, this review intends to summarize published findings related to camel cellular immunology with a focus on the phenotype and functionality of camel leukocyte subpopulations. The review also describes the impact of different physiological (age and pregnancy) and pathological (e.g. infection) conditions on camel immune cells. Despite the progress achieved in the field of camel immunology, there are gaps in our complete understanding of the camel immune system. Questions remain regarding innate recognition mechanisms, the functional characterization of antigen-presenting cells, and the characterization of camel NK and cytotoxic T cells.

Keywords: camel (*Camelus dromedarius*), immune, overview, review—systematic, leukocytes, monocyte subpopulations

INTRODUCTION

Camels (*Camelus* spp.) are essential inhabitants of desert and semi-desert ecosystems (1). Unlike many other domestic species, camels thrive despite extreme temperatures, scarce vegetation, and very limited food and water resources (2, 3). The family of Camelidae comprises two major subfamilies, namely Camelinae (Old World camelids) and Laminae (New World camelids). The Old World camelids include two domesticated species: the dromedary or one humped camel (*Camelus dromedarius*) and the two humped camel or Bactrian camel (*Camelus bactrianus*) (4, 5). The wild camel (*Camelus ferus*) is a third species of Old World camelids, which is a double-humped camel living in central Asia and closely related to the Bactrian camel (6). The New World camelids, which live in the high altitudes of South America, comprise four main species including two wild species (guanaco and vicuña) and two domesticated species (llama and alpaca) (7).

In addition to their economic importance as domestic food animals in many regions of the world including the Middle East, different parts of Africa, and most regions of Asia (8, 9), camels are also found in circus or zoological collections in the northern hemisphere (10). Camels are of zoonotic importance due to many pathogens that can be transmitted to humans. For example, dromedary camels are considered as the main reservoir for the lethal zoonotic coronavirus, which is responsible for Middle East Respiratory Syndrome (MERS) in humans (11).

The immune system consists of a complex network of cellular and non-cellular components, which contribute equally to effective immune responses against pathogens. Whereas considerable research has been devoted to studying camel immunoglobulins (12), rather less attention has been paid to the cellular compartment of the camel immune system. As the progress achieved in the analysis of camel immunoglobulins has previously been covered in many recent reviews (5, 12–14), the present review will highlight the most important findings concerning camel cellular immunology. The review will especially focus on recent phenotyping and functional studies characterizing camel blood leukocyte subpopulations. In addition, the impact of different physiological (age and pregnancy) and pathological (e.g. infection) conditions on the cellular immune compartment will be discussed.

In comparison to other species from the same geographical area, camels show higher resistance to some infectious diseases and environmental stress (15–19). Compared to the severe course of many Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in humans, camels show only mild and transient respiratory symptoms with no need for veterinary care (15, 16). Possible mechanisms for the higher resistance of camels to MERS-CoV are discussed below (*The camel immune response to MERS-CoV*). Dromedary camels also appeared to be resistant to infectious doses of foot-and-mouth disease virus (FMDV), which were sufficient to infect sheep in the same experiment (18). This type of resistance is species-dependent, since FMDV is more infectious for Bactrian than for dromedary camels (18). FMDV utilizes different integrin heterodimers ($\alpha\nu\beta 1$, $\alpha\nu\beta 3$, $\alpha\nu\beta 6$, and $\alpha\nu\beta 8$) as cellular receptors (20). Whether these integrins are differentially expressed or regulated in the susceptible and resistant species, and whether the higher resistance of camels to FMDV is determined at the level of virus-integrin interaction, represents an important question that has yet to be addressed. Dromedary camels are also well adapted to extreme levels of heat stress (19). Compared to humans, this may rely on a faster, stronger and differential induction of heat-shock protein family members and the higher resistance of general protein synthesis in response to thermal stress (21, 22). Deeper insights into the mechanisms behind the higher resistance of camels to some infectious agents and the adaptation of camel immune cells towards thermal stress are still pending.

Several immunogenomic studies described the genomic diversity of immunity-related genes in domesticated and wild camels, including genes encoding for B cell receptors, T cell receptors, and MHC molecules (6, 23–29).

THE LEUKOGRAM PATTERN OF CAMELS IN HEALTH AND DISEASE

The species-specific leukogram, which comprises the total white blood cell (WBC) count and the relative proportions of the main leukocyte subpopulation including neutrophils, eosinophils, basophils, lymphocytes, and monocytes, provides a cost-effective evaluation tool in human and veterinary medicine,

supporting disease diagnosis and guiding therapy and prognosis prediction.

A broad total WBC count range in the healthy dromedary camel, from 8.3 to 19.6 cell $\times 10^3/\mu\text{l}$ blood, has been reported in the literature (30, 31). Lower (32) as well as higher (33) WBC counts were reported for the Bactrian camel in comparison to the dromedary camel. In general, camels have a higher WBC count than domestic ruminants (33, 34). This is mainly due to higher numbers of neutrophils in camel blood. The fraction of neutrophils among blood leukocytes accounts for up to 77% followed by lymphocytes (30% on average) (32, 35–38). This is in contrast to domestic ruminants, where lymphocytes outnumber the leukocyte population in blood (33). The dominance of neutrophils among camel blood leukocytes results on average in a very high neutrophils to lymphocyte ratio (NLR) of 5:1 compared to a NLR of 1:2 found in domestic ruminants (39, 40). The NLR is a novel marker which has been found to be associated with systemic inflammatory responses (41–44). In other species, high NLR has been linked to impaired immune cell function and was indicative of poor patient survival in different diseases including sepsis (45, 46) and autoimmune diseases (47). The clinical relevance of the relatively high NLR in camels and its impact on the functionality of the camel immune system still needs to be investigated.

Historically, there has been a great deal of discrepancy in the literature regarding leukocyte composition in camels, depending on the techniques used to analyze the samples. Earlier studies mostly applied hemocytometers to estimate the camel leukogram with settings adapted from other species. According to those studies, lymphocytes represent the most abundant leukocyte subpopulation in camel blood followed by neutrophils (48–54). However, recent hemocytometer and flow cytometric studies (55–57) identified neutrophils as the main fraction of camel leukocytes (36, 58–62).

Numerous studies investigated the changes in the camel leukogram pattern under different physiologic (age, sex, pregnancy) (63–65) and pathologic (infection) conditions (66, 67). As most camel leukogram studies presented leukocyte composition as relative values (fractions) rather than absolute values, it is difficult to compare the results obtained from different studies.

Impact of Animal Age and Sex on the Camel Leukogram

The impact of age on the camel leukogram has been described in different studies (35, 68). In comparison to adults, young camels show higher WBC counts with higher percentages of lymphocytes and eosinophilic granulocytes but lower percentage of neutrophilic granulocytes (35). The leukogram pattern of the newborn camel calf is discussed below in detail.

Although some studies reported higher WBC counts in male camels (69), in general the animal sex shows no impact on total WBC count or differential leukocyte composition (32, 70, 71). Some authors reported a higher proportion of lymphocytes among leukocytes in males compared to female camels (70, 72), while the eosinophil fraction was higher in females compared to males (70).

The impact of pregnancy on the camel leukogram (60) and the detailed immunophenotype of leukocytes in pregnant she-camels will be discussed in a separate section below.

Seasonal Effects on the Camel Leukogram

There have been inconsistent observations regarding the impact of seasonal effects on the camel leukogram (70, 72, 73). For instance, according to Mehrotra and Gupta (74), the number of leukocytes tends to decline during the summer season. In contrast, Babeker et al. reported higher numbers of WBC with increased total numbers of neutrophils, lymphocytes, eosinophils, and basophils in camel blood during the summer season in comparison to the winter (73).

The Camel Leukogram Pattern During Infectious Diseases

Changes in leukocytes count and composition during different parasitic and bacterial infections have been frequently described. For example, trypanosomiasis in camels induces a marked increase in the number of WBC with increased percentages of neutrophils and reduced percentages of lymphocytes (49). Relative eosinophilia (elevated fraction of eosinophils in blood) has been reported in camels suffering from different parasitic infestations, including *Trypanosoma evansi* (75), gastrointestinal helminths (71), and nasal *Cephalopina titillator* (76). In camels infected with the blood parasite *Theileria anulata*, the leukogram pattern was characterized by leukocytosis, neutrophilia, eosinophilia, and lymphopenia (67). Bacterial pathogens are mainly responsible for post-partal infections in camels, including mastitis and metritis (77–80). The leukogram pattern associated with camel endometritis has been described for the clinical and subclinical form of the disease. Clinical endometritis in camels is characterized by a significant rise in the total cell count of blood leukocytes, which is mainly due to higher cell numbers of neutrophils (37, 81). However, in the case of subclinical endometritis she-camels did not show a different leukogram in comparison to healthy animals (82).

CHARACTERIZATION OF PHENOTYPE AND FUNCTION OF CAMEL LEUKOCYTE SUBPOPULATIONS

Early attempts to study the cellular immune system in camels were hampered by the limited availability of camel-specific monoclonal antibodies (83, 84). As the production of monoclonal antibodies is a very costly process, attempts have been made to evaluate the cross-reactivity of commercially available monoclonal antibodies raised against leukocyte antigens of ruminants, swine, or human, with camel leukocyte antigens. Using the identified cross-reactive antibodies (Table 1) and flow cytometry, several camel myeloid and lymphoid immune cell populations and subpopulations have been recently characterized (59, 83–85, 87–89). The antibody toolbox for camel leukocyte antigens includes antibodies to several myeloid markers such as CD172a, CD14, and CD163, and major histocompatibility complex (MHC) class I and II molecules. Using those monoclonal antibodies in combination

TABLE 1 | Camel leukocyte antigen cross-reactive monoclonal antibodies.

Antigen	Clone	Isotype	Source
CD4	GC50A1	mlgM	WSU
CD11a	G43-25B	mlgG2a	BD
CD11a	HUH73A	mlgG1	WSU
CD11b	ICRF44	mlgG1	BD
CD14	TÜK4	mlgG2a	Biorad
CD14	M5E2	mlgG2a	BD
CD14	CAM36A	mlgG1	WSU
CD18	6.7	mlgG1	BD
CD18	HUH82A	mlgG2a	WSU
CD26	polyclonal	glgG	R&D systems
CD44	LT41A	mlgG2a	WSU
CD45	LT12A	mlgG2a	WSU
CD62L	MEL14	mlgG2a	Biologend
CD163	LND68A	mlgG1	Kingfisher
CD172a	DH59b	mlgG1	WSU
B cells	GC26A	mlgM	WSU
MHCI	H58A	mlgG2a	WSU
MHCII	TH81A5	mlgG2a	WSU
MHCII	TH14B	mlgG2a	WSU
MHCII	L243	mlgG2a	BD
WC1	BAQ128A	mlgG1	Kingfisher
WC1N2	BAQ4A	mlgG1	WSU
Activation marker	LH9A	mlgM	WSU
Activation marker	VPM30	mlgM	Biorad

MHC, Major Histocompatibility Complex; WSU, Washington State University; BD, Becton Dickinson; mlgM, mouse immunoglobulin M; mlgG, mouse immunoglobulin G; glgG, goat IgG (36, 59, 61, 85, 86).

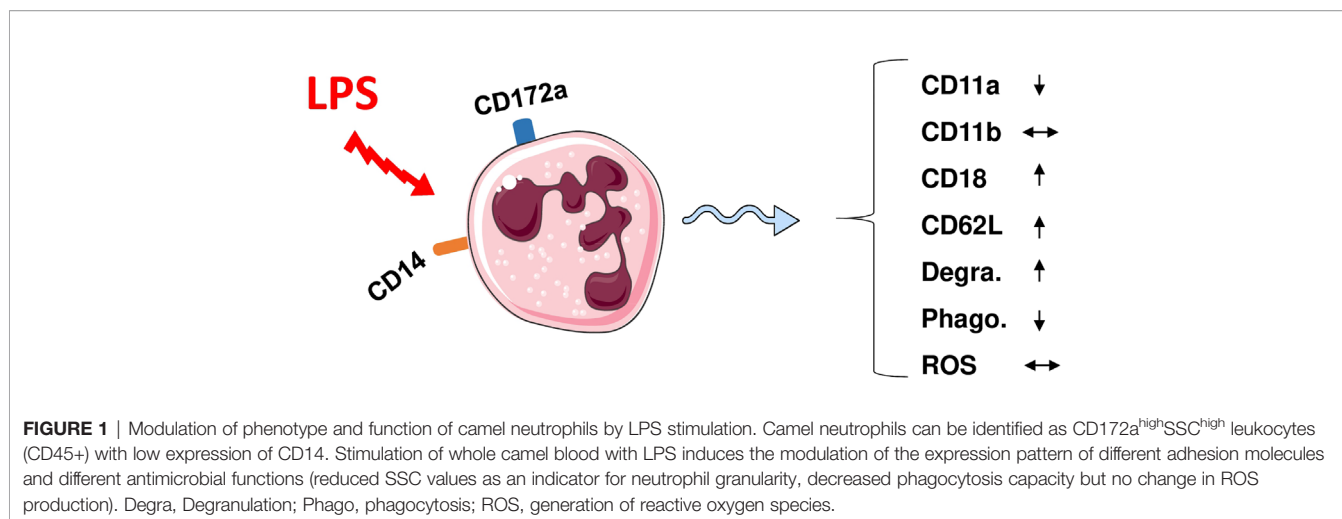
with antibodies against cell adhesion molecules (CD11a, CD11b, CD18, and CD62L) has enabled the characterization of camel monocyte subsets. Monoclonal antibodies specific for CD4 and WC1 molecules allowed for the characterization of camel CD4-positive T cells and $\gamma\delta$ -T cells. The characterization of other important lymphocyte subpopulation, especially CD8-positive T cells and NK cells, still requires the identification of monoclonal antibodies to camel CD8 and CD335 (NKP46) molecules.

Camel Neutrophilic Granulocytes

Flow cytometric analyses identified camel blood neutrophils as highly complex/granular cells (side scatter, SSC^{high}) expressing CD45 and CD172a (35, 62). The higher green autofluorescence of eosinophils can be used to differentiate between camel eosinophils and neutrophils within the granulocyte population (35, 60).

Neutrophil recruitment is a cascade process organized by a set of cell adhesion molecules, which mediate their adhesion to endothelial cells of blood vessels and the subsequent steps of extravasation (90). Compared with human neutrophils, dromedary camel neutrophils express similar levels of the integrins LFA1 (CD11b/CD18) and MAC1 (also known as α M β 2; CD11b/CD18) (59).

Similar to bovine neutrophils (91), camel neutrophils show a low but distinct expression level of the LPS co-receptor CD14, suggesting a role in the sensing of gram-negative bacteria (35). This has been partially proven in whole blood stimulation assays (Figure 1) where LPS induced the activation and degranulation of camel neutrophils. In addition, LPS stimulation reduced the phagocytosis activity of camel neutrophils, while their ROS generating potential remained unchanged (62).



A series of recent studies on human neutrophils has indicated that distinct neutrophil subsets exist within the whole neutrophil population with diverse roles in infection and inflammation (92–95). For the camel, the heterogeneity of blood neutrophils remains an open issue. In addition, the interplay between camel neutrophils and other innate immune cells such as monocyte subsets and macrophages (96) has not yet been studied.

Camel Monocyte Subsets

Monocytes are circulating immune cells with an essential role in the innate immune defense against pathogens (97). Upon migration into tissues, monocytes are responsible for the replenishment of other immune cells of the mononuclear phagocyte system including macrophages and dendritic cells, which bridge the innate and adaptive immune responses (98, 99). For their effective antimicrobial functions, monocytes are equipped with several receptors enabling pathogen sensing, engulfment, and elimination (100, 101). The cell surface cluster of differentiation (CD) antigens CD172a, CD14, CD16, CD163, and MHCII have been proven as reliable markers to describe monocyte heterogeneity, their functional status, and their polarized differentiation into distinct macrophage subtypes (102–105). CD172a, which is known as signal-regulatory protein alpha (SIRPa), is a glycosylated cell surface receptor expressed on myeloid cells and functions as a regulatory receptor that inhibits cell signaling (106). CD14 is membrane protein mainly expressed on monocytes and functions with TLR-4 as a bacterial pattern recognition receptor responsible for binding lipopolysaccharide (LPS), the cell wall component of gram-negative bacteria (107). CD163 is a scavenger receptor for haptoglobin-hemoglobin complexes that is mainly expressed on monocytes and macrophages and is considered as a marker for anti-inflammatory functional subtypes of these cells (108). Major histocompatibility (MHC) class II molecules are antigen receptors expressed on blood monocytes and B cells and present antigens to T helper cells (109).

Due to the lack of monoclonal antibodies cross-reactive with camel CD16 (59), three subpopulations of monocytes in dromedary camels have recently been identified based on the expression profiles of CD172a, CD14, MHCII, and CD163 (61). Similar to

the porcine and bovine systems (104, 106, 110–112), the signal-regulatory protein alpha (CD172a) has been identified as a pan monocyte marker for camel monocytes. The most abundant subset of camel monocytes (87% of total monocytes) expresses high levels of CD14 and CD163, but low levels of MHCII (CD14^{high}CD163^{high}MHCII^{low}) and is classified as camel monocyte (cMo)-I. A small fraction of camel monocytes (6 % of total monocytes) expresses high levels of CD14, CD163, and MHCII (CD14^{high}CD163^{high}MHCII^{high}) and is designated as cMo-II. The third minor monocyte subpopulation cMo-III (5 % of total monocytes) displays high expression of MHCII but low expression of CD14 and CD163 (CD14^{low}CD163^{low}MHCII^{high}) (61) (Figure 2).

Different monocyte classification systems have been used in different species (113). Human and bovine monocytes were classified into the major population of CD14⁺⁺ CD16⁻ classical monocytes and two minor populations of CD14⁺⁺ CD16⁺ intermediate monocytes and CD14⁺ CD16⁺⁺ non-classical monocytes (104, 106, 112, 114, 115). Due to their low expression of CD14, murine monocytes were classified into three subsets based on their expression of the myeloid markers Ly6C and CD43 (116, 117). Whereas for the analysis of monocyte heterogeneity in the pig (110, 118) and the dog (119), other monocytic markers including CD163, CD172a and MHCII have been used.

The expression of high levels of CD14 and CD163 on cMo-I and the low MHCII expression together with their dominance among all blood monocytes suggests close similarity with bovine and human classical monocytes (104, 115). The phenotypic and functional properties (highest anti-bacterial activity) of cMo-II suggests this subset is an equivalent to human and bovine intermediate monocytes (106, 113). Similarly, high levels of surface MHCII and adhesion molecule leukocyte function-associated antigen (LFA)-1 (α 1 β 2; β 2 integrin; CD11a/CD18) and the low expression density of surface CD14 and CD163 together with a reduced phagocytic and ROS generation activity, suggest that cMo-III represent the counterparts of bovine non-classical monocytes (96, 104, 106).

In a recent report, the clinical relevance of camel monocyte subsets in camel clinical endometritis has been investigated (81).

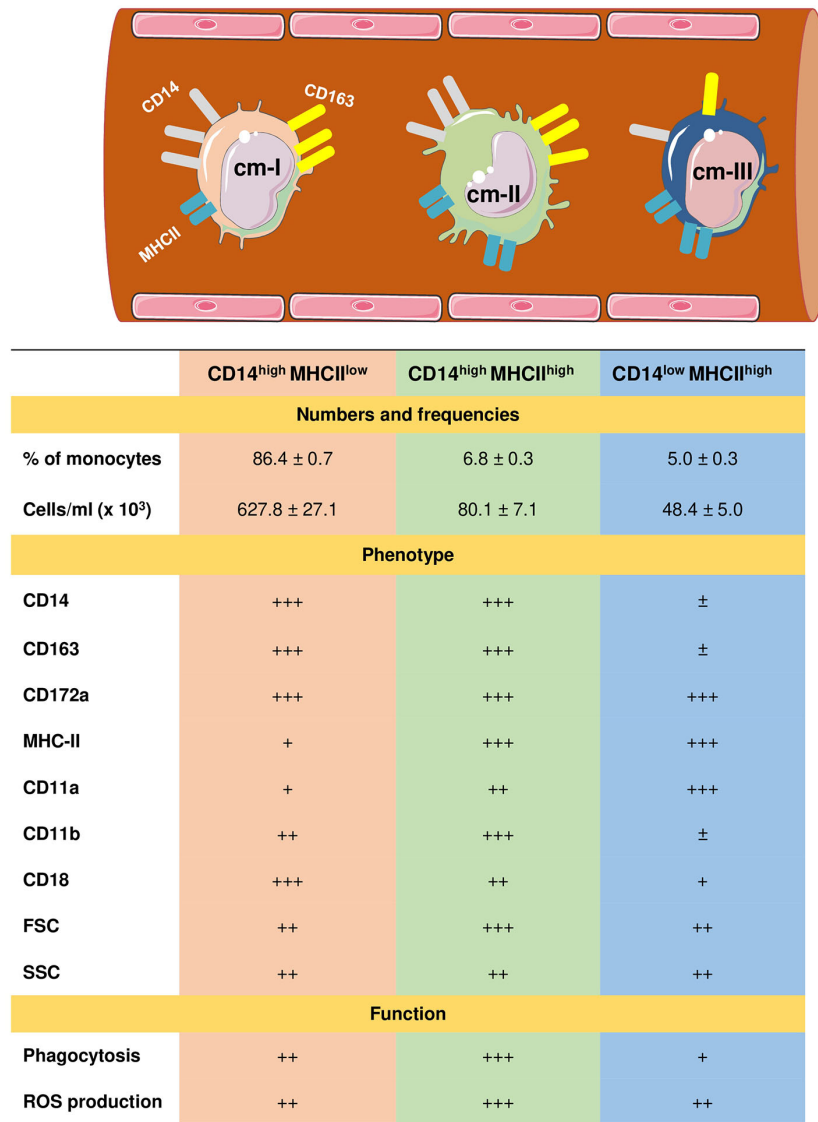


FIGURE 2 | Heterogeneity of camel monocyte subsets. Camel monocytes are subdivided according to the surface expression of CD14 and MHCII into three monocyte subsets. (1) Camel monocyte I (cM-I) with high expression of CD14 and low expression of MHCII (CD14^{high}MHCII^{low}), cM-II with high levels of both CD14 and MHCII (CD14^{high}MHCII^{high}) and cM-III with high expression of MHCII but low expression of CD14 (CD14^{low}MHCII^{high}). The expression levels of cell surface molecules are presented as ± for very low to no-expression, + for weak expression, ++ for intermediate expression, and +++ for high expression. Functional capacities of monocyte subsets are presented as + for weak, ++ for intermediate, and +++ for strong capacity.

In this study, animals with endometritis showed a significant expansion in the fraction of camel inflammatory monocytes (cMo-II). In addition, increased numbers of cMo-II were indicative for the severity of endometritis. The study suggested camel cMo-II as a disease biomarker for clinical endometritis in camels (81).

Camel monocytes appear to be the only leukocyte population that exclusively express CD26, the MersCoV receptor and are therefore suggested to play a key role in either disease pathogenesis or immune response to the virus (86, 120). Whether the mentioned camel monocyte subsets differ in their expression intensity of CD26 is unknown. More work is needed to further

explore the subset-specific function in health and disease for camels as for human and bovine monocyte subsets. Their role in the pathogenesis of different infectious and non-infectious diseases has been indicated in a series of recent studies (121–124). A further open question is, whether camel monocytes show subset-specific potential to differentiate into distinct functional subsets of macrophages or dendritic cells.

Camel Lymphoid Cell Subpopulations

Due to the lack of camel-specific antibodies, only selected subpopulations of camel lymphoid cells are identifiable. Thus, a comparison of camel lymphoid cell populations with cells of other

domestic animal species and humans is very limited. Notably, CD8+ T-cells, cytotoxic T cells and NK cells cannot be identified in camels, which severely inhibits the analysis of anti-viral and vaccination responses. Based on the TCR type, T cells are divided into $\alpha\beta$ T cells recognizing peptide antigens presented on MHC molecules and $\gamma\delta$ T cells recognizing antigen epitopes in an MHC independent manner (125). Using monoclonal antibodies cross-reactive to the camel CD4 antigen, the bovine $\gamma\delta$ T cell marker WC1, the B cell antigen GC26A together with monoclonal antibodies specific to CD14 to exclude monocytes, it was possible to identify camel CD4-positive T cells, WC1-positive $\gamma\delta$ T cells, and GC26A-positive B cells in the blood of dromedary camels (Table 2) (36).

In healthy dromedary camels, blood lymphocytes are composed of a major fraction of B cells (mean percentage of 26.6%) followed by CD4-positive T cells (24.6%) and a minor fraction of $\gamma\delta$ -T cells (7.4%) (36). In comparison to their nearest relatives (Lamini), healthy camels show some similarities in their lymphocyte composition (126, 127). Similar to their dominance among camel blood lymphocytes, B cells represent the main lymphocyte population in blood from healthy alpacas (126, 127). In addition, the fractions of CD4+ T cells and $\gamma\delta$ -T cells in blood from alpacas (126, 127) and dromedary camels (36) are comparable. It is unknown, whether camel CD8+ T cells are present in the same frequency as in blood of alpacas (126, 127). The significant expansion of CD8+ T cells in the gut-associated lymphoid tissue (GALT) of alpacas 9 days postinfection with bovine virus diarrhea virus (BVDV) indicates a key role for this lymphocyte subset in the immune response of camelids to viral infections (127).

The analysis of the expression pattern of the adhesion molecules CD11a, CD11b, CD18, and CD62L, which play essential roles in lymphocyte trafficking to peripheral tissues (128), revealed similar expression patterns on camel and bovine CD4+ T cells and $\gamma\delta$ T cells (36, 129).

T helper cells are key players in the adaptive immune response through their essential role in managing both humoral and cell-mediated immune responses. Upon antigen-specific stimulation,

naïve CD4+ T cells differentiate into effector T helper cells, which can be distinguished based on the differential expression of cell surface adhesion molecules such as CD45, CD44, CD62L, and CD11a (130–134). Similar to their human counterparts (135), camel naïve (CD11a^{low} CD44^{low}) and effector (CD11a^{hi} CD44^{hi}) T helper cells have recently been identified with an elevated proportion of effector T helper cells in animals with respiratory infections (23.5% of total CD4-positive lymphocytes compared to 17.1% in healthy camels) (36).

Camel Cytokines

Functional properties of camel lymphocyte subpopulations have not been investigated so far. Especially the characterization of camel subsets of helper T cells and the innate signals required for their functional polarization into Th1, Th2, or Th17 subsets requires further investigation. T cell polarization is one of the key factors that determine the outcome of infectious diseases (136). The characterization of T effector cell subsets is limited by the lack of monoclonal antibodies specific for camel Th1, Th2, and Th17 cytokines. The characterized genes of Th1 (IL-2, IL-12, and IFN- γ) and Th2 (IL-4, IL-10 and IL-13) cytokines in the Bactrian camel (137, 138), however, could represent a valuable tool for conducting functional studies on T cell polarization in camels. The high homology between Bactrian camels and other species, including the llama, pig, cow, and horse regarding the nucleotide sequences of their cytokine genes (137) also suggests the necessity of testing monoclonal antibodies specific for cytokines of these species for their cross-reactivity with camel cytokines. However, the lack of characterized camel antigen-presenting cells and the establishment of *in vitro* systems for the differentiation of camel monocyte-derived macrophages and monocyte-derived dendritic cells hamper antigen-specific activation and T-cell polarization studies.

Studies on cytokine responses *in vivo* relied on the measurement of mRNA expression. Bactrian camels vaccinated with a live attenuated *Brucella abortus* S19 vaccine responded with an upregulated expression of the Th-1 cytokine IFN γ with low or no expression of the Th2 cytokines IL-10 and IL-4, indicating the activation of a cell-mediated immune response (138). To address

TABLE 2 | Phenotypic properties of T cells and B cells in camel blood.

	CD4+ T cells (CD4 ⁺ WC1 ⁺)	$\gamma\delta$ T cells (WC1 ⁺ CD4 ⁺)	B cells (GC26A ⁺ MHC-II ⁺ CD14 ⁺)
Frequency in blood			
% of lymphocytes (Mean \pm SEM)	24.6 \pm 1.7	7.4 \pm 0.3	26.6 \pm 1.9
% of lymphocytes (Min. – Max.)	14.2–33.1	1.0–20.1	18.4–42.0
Phenotype			
CD4	+++	–	–
WC1	–	+++	–
GC26A	–	–	+++
MHC-II	–	–	+++
CD18	++	++	?
CD11a	++	++	?
CD11b	+	++	?
CD62L	+	++	?
Effector cells	CD11a ^{high} CD44 ^{high} (17.0 \pm 1.2) %	?	?

The expression levels of cell surface molecules are presented as - for very low to no-expression, + for weak expression, ++ for intermediate expression, and +++ for high expression. Non investigated parameters are presented as ? (36).

the humoral immune response and the production of antigen-specific antibodies, a recent immunization study with ovalbumin proved that the upregulated cytokine expression pattern of Bactrian camel lymphocytes was restricted to Th-2 cytokines (IL-4, IL-10, and IL-13) (139). At present, these studies basically indicate a high degree of similarity in the polarized cytokine response towards vaccines and antigens in other mammalian species, namely cattle (140, 141).

Type I interferons represent the most important cytokines in innate immunity during infections with viruses in addition to antitumor immune responses. The camel displays a similar broad spectrum of IFN alpha family members as cattle (142) and humans (143). For instance, eleven IFN- α subtypes (144) and one member of the IFN epsilon family were identified (145). The functional properties of type I interferons appear similar to other mammalian species, including the antiviral effect, the induction of interferon-responsive genes, and the tumor cell cytotoxicity (144, 145). Studies describing other immunomodulatory effects of type I interferons are still lacking (145).

CAMEL IMMUNOGENETICS

In comparison to other species inhabiting the same geographical area, camels are more resistant to some pathogens (4, 15, 16, 18, 146). The ability to respond to a variety of antigens is affected by the diversity of highly specialized antigen receptors (147). This has been addressed in a series of immunogenomic studies which investigated the polymorphism of genes encoding different camel antigenic receptors, including the $\alpha\beta$ and $\gamma\delta$ T cell receptor, the NK cell receptor, and the antigen-presenting molecules MHC-class I and class II.

In comparison to other Artiodactyls, dromedary camels display a limited repertoire of T cell receptor delta variable (TRDV) and T cell receptor gamma variable (TRGV) genes (26). However, the diversity of the camel dromedary $\gamma\delta$ T cell repertoire is significantly expanded by somatic hypermutation of the TRDV and TRGV genes (27, 28, 148). The diversity of the variable domains of the $\alpha\beta$ T cell receptor is formed only by classical combinatorial and junctional diversity and not by somatic hypermutation (148).

Antigen recognition by T cell receptors on CD4+ or CD8+ T cells requires the presentation of antigenic peptides by MHC class II or class I molecules respectively (149, 150). As those polymorphic antigen-presenting molecules display promiscuous and selective interactions with antigen peptides, diversity in genes and alleles encoding for MHC class I and class II molecules contributes directly to the ability of a species to respond towards a range of different pathogens (150). In a recent report, Plasil and coworkers investigated the localization, organization, and sequence of camel MHC genes (23). MHC genes are located on chromosome 20 in camels and are organized in MHC class II, MHC class III, and MHC class I genes, an organization that follows the same pattern as in other mammalian species (148). The camel MHC genomic structure more closely resembles the porcine rather than the bovine MHC. Compared with other mammalian

species, however, camels show a significantly lower molecular diversity of both MHC class I and class II genes (23, 24).

Natural killer (NK) cells are innate lymphoid cells with key roles in innate immune responses against intracellular pathogens and tumor cells. These multiple functions are mediated by different activating and inhibitory NK cell surface receptors, which determine the activation status of an individual NK cell (151). A recent work by Futas et al. investigated the diversity of gene families encoding the camel NK cell receptors, including the natural killer complex (NKC) and the leukocyte receptor complex (LRC), which mediate their function through the interaction with MHC class I molecules (25). Collectively, the study identified a low polymorphism of the killer-cell immunoglobulin-like receptors (KLR) genes in camels, which is similar to the polymorphism of this complex in the domestic pig. The study also revealed important differences in the genomic organization and polymorphism of genes encoding NK cell receptors between camels and cattle (25).

Recently, high quality genome assemblies have been developed for domestic and wild camel species (6, 29). Computational methods were employed for the improvement of genome assemblies of the three Old World camel species (6). The authors used the upgraded genome assemblies to investigate nucleotide diversity of immune response genes in the three species. The highest mean nucleotide diversity was identified in the domestic Bactrian camel. The comparison between several innate and adaptive immune response gene groups revealed the highest mean nucleotide diversity in the major histocompatibility complex (6).

The overall reduced antigen receptor diversity and MHC polymorphism, however, indicates the existence of other mechanisms responsible for the higher resistance of camels to infectious diseases. Whether camel-specific epigenetic regulatory mechanisms of adaptive immune responses contribute to the relatively higher resistance to infections is currently unknown.

THE IMMUNE SYSTEM OF THE PREGNANT SHE-CAMEL

Pregnancy is a physiologic condition, usually associated with modulations in different immune mechanisms, which ensure protection against pathogens and at the same time prevent immune mediated destruction of the conceptus (152–154). Immunomodulation during pregnancy is not restricted to the local uterine environment but extends also into the periphery (155, 156). Pregnancy-associated immunomodulation has been addressed by a large number of studies in pregnant women (157), cows (158, 159), mares (160, 161), and sows (162–165). A recent study investigated the impact of pregnancy on the phenotype and function of she-camel blood leukocytes (60). The observed significant leukocytosis of pregnant she-camels is similar to findings reported for pregnant cows (166) and women (167), which is usually linked with an increased cortisol level during pregnancy (161). According to the same study, the leukocytosis in pregnant she-camels is characterized by a reduced neutrophil fraction and higher percentages of lymphocytes and monocytes.

This leukocyte composition pattern, however, differs from the pattern reported for pregnant cows (162). In cows, pregnancy is associated with higher fractions of neutrophils, lower fractions of lymphocytes but no changes in the fractions of monocytes (166, 168).

Although not proven, it was suggested that the enhanced neutrophil extravasation and accumulation in the uterine tissue might be responsible for the decreased proportion of neutrophils in the blood, as neutrophils from pregnant animals expressed higher densities of the cell adhesion molecule LFA-1 on their surface than non-pregnant animals (60). Ex vivo functional analyses revealed an enhanced antimicrobial activity of neutrophils from pregnant she-camels. This finding is in line with reports of pregnant mares (169), but is opposite to the dairy cow, where pregnancy is associated with impaired antimicrobial functions of neutrophils (170, 171).

THE IMMUNE SYSTEM OF THE NEWBORN CAMEL CALF

Similar to horses, pigs, and ruminants, the epitheliochorial placenta of camels does not allow trans-placental passage of maternal immunoglobulins to the fetus (172, 173). Therefore, the newborn camel calf is born without serum immunoglobulins and postnatal protection mainly relies on an adequate absorption of maternal colostrum antibodies until the maturation of the calf's own immune system (174, 175). The transfer of colostrum immunoglobulins to the newborn camel calf has been subject of many investigations (176–182). Several immunoglobulin classes, including the IgM, IgG, and IgA, have been identified in the camel colostrum (182). However, only the uptake of maternal IgG, representing the most abundant immunoglobulin in camel colostrum, into the newborn's blood has been studied.

In addition to the conventional IgG with its heterodimeric structure, camelids also possess non-conventional single-chain IgG antibodies, which are not found in any other mammalian species (183). In contrast to conventional IgG structure, which consists of two identical heavy chains (H) and two identical light chains (L), camel single-chain IgG antibodies are devoid of the light chain and the first heavy chain constant region CH1. The camel IgG isotype is currently classified into three structurally different subclasses: camel IgG1 with two light and two heavy chains, camel IgG2 with a long-hinge heavy chain, and camel IgG3 with a short-hinge heavy chain (**Figure 3**). The camel heavy-chain antibodies (HCAbs) IgG2 and IgG3, which lack light chains, contribute up to 75% of all serum IgG (13).

Both classical two-chain antibodies (IgG1) and HCAbs (IgG2 and IgG3) are present in camel colostrum (182), and both are involved in the passive transfer of colostrum IgG antibodies to the newborn calf (178, 179). Some studies investigated the development of IgG (176) and HCAbs (178) in the blood of the newborn camel calf. The rise in serum IgG levels in calf serum two months after birth is indicative of the production of significant levels of the calf's own IgG (177, 184). The role of maternal colostrum cells in neonatal immune system development, and their responses to vaccination is of growing

interest in other species (185–190). However, no studies have yet been conducted on the role of colostrum immune cells in the modulation of the camel calf immune system.

Age-related changes of innate and adaptive cellular immune responses have been described for different species (191, 192). The immaturity of newborn immune cells was linked to a higher susceptibility to infectious diseases and higher mortality rates during the early weeks after birth (191, 193–200). As in other ruminants, camel newborns and adult camels differ significantly regarding their leukogram pattern, phenotype and functionality of blood leukocyte subpopulations (201). During their first month of life, the leukogram pattern of newborn camel calves is characterized by higher leukocyte numbers, higher numbers of neutrophils, monocytes, and lymphocytes, but lower numbers of eosinophils in comparison to adult camels (201). The reduced numbers of eosinophils in newborn camel calves, which play a major role in parasitic immunity (39), has been related to lower parasitic manifestation in comparison to adults (202).

High neutrophil to lymphocyte ratio (NLR) has been linked to impaired immune cell function and poor patient survival in different inflammatory diseases (45–47). Camel calves are born with a higher NLR (12.1 in average) than found in adults (5.1 in average) (184). NLRs drop within two months after birth to adult camel values. It was suggested that initially high calf NLRs reflect the pro-inflammatory nature of newborn camel immune responses and a shift towards mature and correctly polarized immune responses takes place in the two-month period after birth (184).

Similar to other artiodactyls such as sheep, cows and pigs, with higher frequencies of blood $\gamma\delta$ T cells in younger animals, $\gamma\delta$ T cells account for up to 35% of blood lymphocytes in newborn and young camel calves (36, 70). This indicates that camels belong to the $\gamma\delta$ -high species, in contrast to $\gamma\delta$ -low mammalian species like humans and mice, where $\gamma\delta$ T cells represent only a minor subpopulation (< 5%) of circulating lymphocytes (203).

Compared to adult camels, the fraction of B cells among blood lymphoid cells of newborn camels is higher than in adults, whereas the fraction of CD4+ T cells is lower than in adults (200). The authors discussed a link between elevated numbers of circulating leukocyte populations in camels and their lower expression density of cell adhesion molecules (CD11a, CD11b, CD18) compared to adult leukocytes (201).

Monocytes from newborn and adult camels showed different expression patterns of the monocyte-related surface molecules, CD172a, CD14, CD163 and MHCII (61) (**Figure 4**). Compared to adult camels, newborns display higher numbers of cMo-I and cMo-III, and less numbers of inflammatory cMo-II (61).

Camel calf leukocytes show functional properties that are different from adult camel leukocytes. Flow cytometric analysis of cell granularity and cell size, which are widely used as indicators of the cell activation status (204, 205), revealed a reduced activation potential of calf leukocytes in comparison to adults (120). Phagocytotic activity of newborn neutrophils and monocytes was found to be lower than in adults, with a lower percentage of phagocytosis-positive cells and a reduced number of bacteria ingested per cell (58).

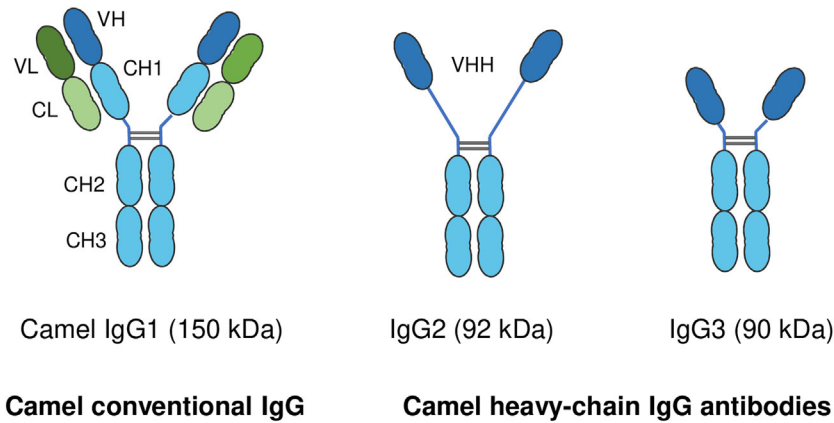


FIGURE 3 | Structure of camel immunoglobulin (Ig) G subclasses. Camel IgGs are currently classified into three structurally different isotypes: Camel IgG1 consists of two identical heavy chains (H) each composed of three constant domains (CH1–CH3) and a single variable domain (VH). Each heavy chain is covalently bound to identical light chains (L) with a constant (CL) and a variable domain (VL). Camel IgG2 and IgG3 are composed of only two identical heavy chains (long-hinge heavy chain in IgG2 and short-hinge heavy chain in IgG3). Camel single-chain IgG subclasses are devoid of the first heavy chain constant region CH1.

Phenotype and function of the main blood leukocyte populations of the newborn camel calf

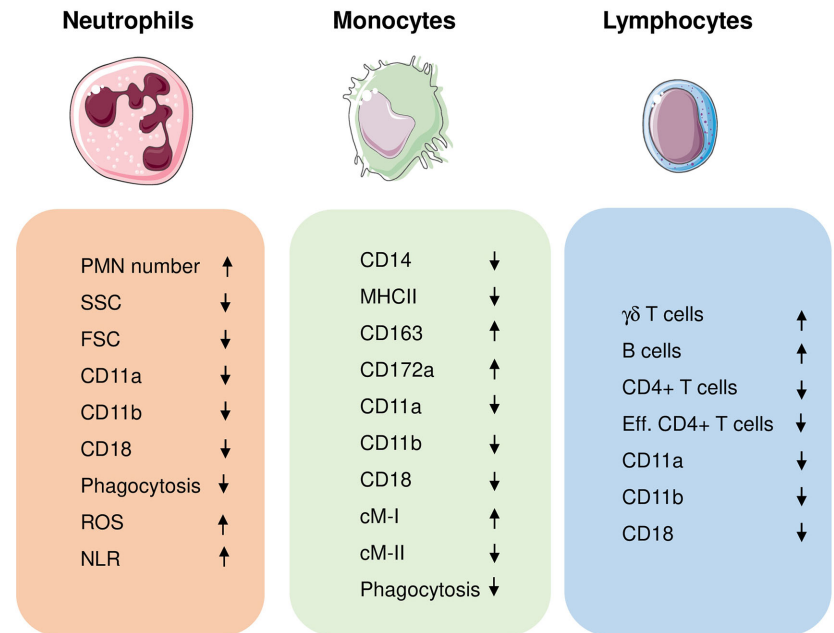


FIGURE 4 | Phenotypic and functional properties of neutrophils (PMN), monocytes, and lymphocytes in blood of newborn camel calves. ROS, Reactive Oxygen Species amount in unstimulated cells; NLR, Neutrophil to lymphocyte ratio; Eff, effector cells. The direction of the arrows indicates higher (up arrow) or lower (down arrow) values for calves compared to adults.

MUCOSAL IMMUNITY IN CAMELS

Mucosal body surfaces are equipped with specialized mucosa-associated lymphoid tissue (MALT), which represent the first

defense barrier of the body preventing infectious agents from invading the internal body tissues (206). Therefore, the characterization of mucosal immune mechanisms has essential impact on the understanding of disease pathogenesis of and the

development of effective vaccines against mucosal infections, including mastitis, metritis, respiratory infections, and gastrointestinal infections. Several studies addressed anatomical structures of the gastrointestinal MALT of Bactrian and dromedary camels (207–211). Detailed and comparative aspects of immune mechanisms on camel body surfaces are still unknown.

The intestine represents the main surface of interaction between the immune system and the huge numbers of microorganisms, which play a pivotal role in guiding the maturation of the mucosal immune system and shaping systemic immunity (212, 213). Morphological studies of the gastrointestinal tract of Bactrian camels revealed a distinct structure and distribution of the MALT in this species (209, 214). Distributed along the whole small intestine, four distinct types of Peyer's patches, including nodular, faviform, cup-shaped, and cystic form Peyer's patches, have been identified in Bactrian camels (214). The nodular and cystic forms of Peyer's patches are unique to this species. The number of Peyer's patches in the small intestine of Bactrian camels increases with age and peaks in 5-year-old camels followed by a subsequent decline (214). Peyer's patches in the large intestine of Bactrian camels are mainly located on the surface of the entire ileocecal orifice, the beginning of the cecum, and the first third of the colon. The ileocecal orifice has been suggested as the main inductive site for mucosal immune responses in the Bactrian camel large intestine (209). In the dromedary camel, Peyer's patches have cup-shaped structures and are distributed in the anti-mesenteric side of the ileum (211). They are not present in the jejunum or duodenum (215). Whether the distinct morphology, structure, and distribution of the MALT structures in camels are reflected by species-specific functional differences of mucosal immune responses, is currently unknown. Mucosal immunoglobulins contribute to the immune homeostasis at the mucosal interface (216). The distribution of secretory IgA (SIgA) and IgG-secreting cells (ISCs) in the lamina propria of the small intestine of Bactrian camels suggests their significant contribution to mucosal immunity in this species (210, 217). Similar to the age-related changes in the number of PP in the intestine of Bactrian camels, SIgA and IgG ISC numbers increase with age with a peak at puberty (210, 217).

The Camel Immune Response to Middle East Respiratory Syndrome Coronavirus

Middle East respiratory syndrome Coronavirus (MERS-CoV) is an emerging zoonotic pathogen that causes the Middle East Respiratory Syndrome (MERS) (11, 218–220). Dromedary camels are considered the only confirmed animal host for MERS-CoV and the source of zoonotic infection (221–228). In humans, MERS-CoV infection is associated with either hospitalization or death, while MERS-CoV-infected camels show only mild and transient respiratory symptoms with no need for veterinary care (15). It is unknown whether special host-pathogen interaction mechanisms in camels contribute to the higher resistance of this species to MERS.

The very high seroprevalence rates (74–100%) of MERS-CoV in camel populations in Africa and the Arabian Peninsula indicate high infection and transmission rates of the virus in camels (16). The dipeptidyl peptidase 4 (DPP4; CD26), a type II transmembrane glycoprotein involved in cleavage of dipeptides and degradation of

incretins (229), has been identified as a functional receptor for the MERS-CoV (230–232). The differential expression of DPP4 in the respiratory tracts of humans and camels has been suggested as the primary cause of limited MERS-CoV replication in the human upper respiratory tract and hence restrict transmission between humans. While DPP4 is only expressed in the human lower respiratory tract epithelium, only the upper respiratory tract epithelium of camels show DPP4 expression (233). Whether the interaction of MERS-CoV with epithelial cells in the lower (human) or upper respiratory tract (camel) results in the secretion of location-specific mediators, which may differently modulate the onset and resolution of subsequent innate and adaptive immune mechanisms, is still an open question.

In opposite to humans, where DPP4 is mainly found on human T lymphocytes rather than monocytes (234), dromedary camels display the highest expression of DPP4 on blood monocytes (86, 120). This may indicate different roles for innate and adaptive immune responses to MERS-CoV in the two species. This is also supported by recent observations on MERS-CoV-infected human individuals, where gradual increases in blood lymphocyte count during MERS progression was observed in all the survivors, whereas the response in diseased patients was characterized by lymphopenia and increased neutrophils and monocytes counts (235).

One of the potential control strategies of MERS-CoV relies on reducing virus transmission from animals to humans through vaccination of camels (223, 236, 237). The development of protective MERS-CoV vaccines for dromedary camels, however, requires an in depth understanding of local immune mechanisms in the respiratory tract in camels and the identification of correlates of protection against the virus. In MERS patients, the development of neutralizing antibodies was not sufficient for an effective clearance of the virus (238). The association between the recovery from MERS and the generation of both antibody and T-cell responses (221, 239) indicates key roles for cell-mediated immune mechanisms against the virus. However, the analysis of immune responses of camels to MERS-CoV infection was limited to the investigation of virus-specific antibodies (179). Studies on cell-mediated immune responses are still lacking. The characterization of camel NK and cytotoxic T cells and their role in anti-viral immunity in the context of infection with MERS-CoV is one of the promising lines of research. MERS-CoV naturally infected camels are currently discussed as a challenge model in vaccine efficacy studies (16). The characterization of mucosal immune mechanisms in the camel respiratory tract, including detailed phenotypic and functional analyses of immune cells in bronchoalveolar lavages and lung parenchymas of MERS-CoV-infected and recovered camels would be a prerequisite for the elucidation of MERS-CoV pathogenesis in these animals.

CONCLUSIONS

The camel represents a multipurpose domestic animal used for meat and milk production, racing, and transportation. Different components of the cellular immune system of the dromedary camel show several species-specific phenotypic and functional properties. In contrast to other domestic species, the camel leukogram is

dominated by the neutrophil fraction resulting in a higher neutrophil to lymphocyte ratio. Camel monocytes are classified into three phenotypically and functionally different subsets based on the expression of the surface molecules CD14 and MHCII with many similarities with the bovine monocyte classification system. Camels belong to the $\gamma\delta$ T cell-high species with especially high percentages of $\gamma\delta$ T cells in newborn and young animals. Circulating camel newborn immune cells contain lower numbers of inflammatory monocytes, show a reduced expression of cell adhesion molecules on all leukocytes, and a reduced antimicrobial functionality of monocytes and neutrophils.

Despite the progress achieved in the field of camel immunology, there are still many gaps towards a more profound understanding of the camel immune system. Open questions cover the innate recognition mechanisms, the functional characterization of macrophages and dendritic cells, and their signals responsible for T cell activation and polarization toward distinct functional subtypes such as type-1, type-2, or type-17 cells. The characterization of camel

NK and cytotoxic T cells and their role in anti-viral immunity, especially in the context of infection with the zoonotic pathogen MERS-CoV is still in its infancy. Promising lines of research would also include host-pathogen interactions on camel mucosal body surfaces such as the respiratory tract, the mammary gland, the uterus, and the intestine.

A deeper characterization of camel infection immunity would help to identify protection-relevant immune mechanisms, essential for the design of effective vaccines, the identification of disease biomarkers, and the selection of animals with higher disease resistance.

AUTHOR CONTRIBUTIONS

JH and HS wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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