Chapter

Goat Immunity to Helminthes

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Abstract

Goat hematology, especially, shares considerable attention since the last 1980s. Large number of discrepant normal hematologic values is reported. The discrepancies resulted came from the differences in age group, breed, and health standing of goats. This makes it further complex with variances in climate of the region, its environment, and size and methodology applied. With time, many inconsistencies, reasonably standardization in normal caprine kinetic hematologic values, are in place. Both goats and sheep are infested by the same key digestive tract helminthes (DTHs) diseases. Helminthes are exceedingly ubiquitous worm parasites that progressed to adopt with many erudite means to evade host immune system.

Keywords: goat, Helminthes, parasites

1. Introduction

Global estimates gathered over time show that goat population is getting bigger as in comparison to sheep numbers. It is estimated that approximately that both share a staggering number of 2.1 billion—over 1.7 billion (80%) resides within Africa and Asia continent [1, 2] and more than 90% of the goat population found in Asia and Africa (**Figure 1**). This increase in goat population is accomplished with its economic value as an efficient converters of low-quality feeds into high quality meat, dairy, and leather products [3, 4].

Goat hematology, especially, shares considerable attention since the last 1980s [5, 6]. Large number of discrepant normal hematologic values is reported. The discrepancies resulted came from differences in age group, breed, and health standing of goats [7]. This makes it further complex with variances in climate of the region, its environment and size and methodology applied. With time, many inconsistencies, reasonably standardization in normal caprine kinetics hematologic values are in place [8–10]. Talking of immune system, specific evidence on the goat immune system remains hard to get as compared to other animal species [11].

Both goats and sheep are infested by the same key digestive tract Helminthes (DTHs) diseases [12]. These parasites are enormously efficacious parasites that affect innate immune response globally around the world [13, 14]. Helminthes are exceedingly ubiquitous worm parasites that progressed to adopt with many erudite means to evade host immune system [15]. They incite pathological features resulting in huge economic losses. Till now most data on the host-parasite interactions are accumulated through ovine (sheep) studies [12, 16]. Helminthes in the abomasum and related area of host still remains as one of the major threats that is responsible for weight loss, anemia, reduced performance and production in goat [17, 18].

In contrast to cattle, many of Cestodes, Trematodes and Nematodes readily cause disease in goat as well as in sheep (**Figure 2**). Recently, some data also highlights differences in caprine and ovine species/strains, especially for nematodes [4, 19]. In goats, it is understood that they tend to accumulate parasites, which is assessed from constant monitoring of increasing number of eggs, keeping in view about seasonal differences in excretion [20]. Sheep acts in reverse [11]. In developed nations, the main magnitudes of these infections is reflected as spartan losses of production. Whereas in underdeveloped/developing countries it translates in more aggravate DTHs mortalities [11, 21].

After goat and sheep domestication, both independently settled down to different feeding habits. The sheep are grazers and prefer to take grass and broad-leafed plant. Goats, on the other hand, are classified as browsers or intermediate browsers. They can ingest substantial amounts of woody plants, vines and brush according to their liking [3]. These feeding habits could upshot to sources of DTHs infestation and with distinct strategies with major consequences to host-parasite relationships [4].

In the caprine evolutionary processes, adaptation to this high miscellany of plants, direct for three consequences to regulate parasitic populations. They include

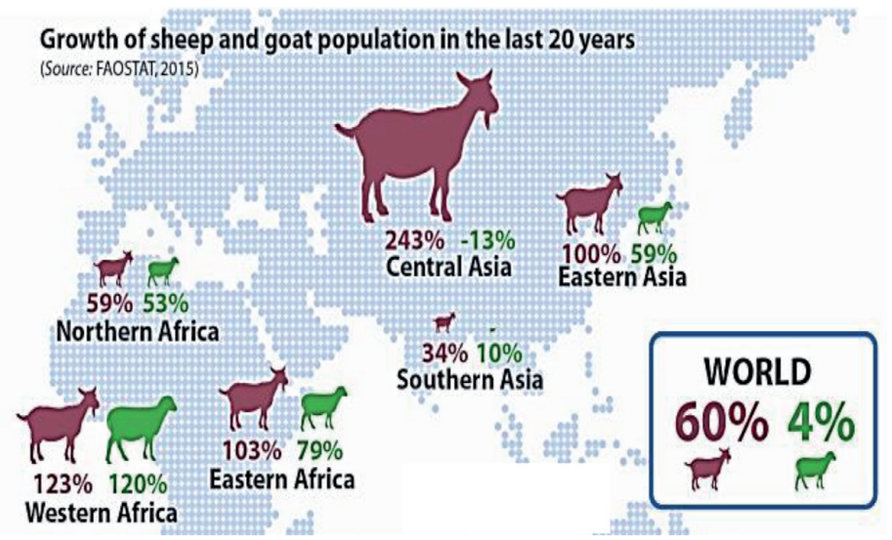


Figure 1.
Growth of sheep and goat population in the last 20 years.

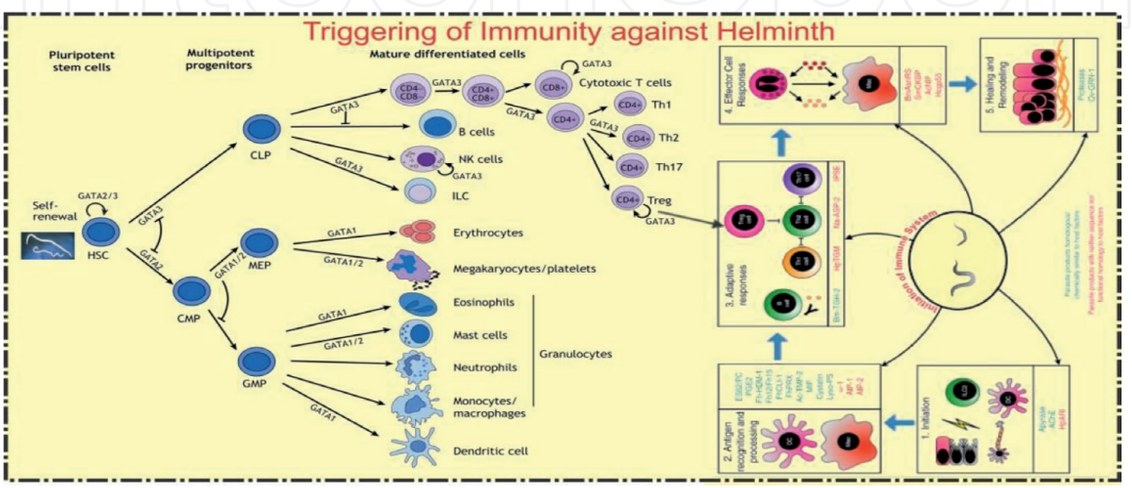


Figure 2.
Developmental stages of immune cells during Helminth infection.

(i) subdued immune response, (ii) increased metabolism of xenobiotics and (iii) self-medication [4]. Recent literature, and documentation show that sheep is studied more to greater depth than to goats. However, generally both species share high degree of genetic and physical similarities [6, 19]. Small differences, however, do exist between the two, such as, goats cannot harbor *Helicobacter pylori* in its gastric lumen. This is in contrary to wide range of animals including sheep and cattle.

2. Research methods and analysis

The method used in this chapter mostly focuses on literature already published or still in draft form. The thorough insight in to literature discussed put some light on the immune response in general and goat immune system in particular for the further areas to be addressed in future studies.

3. Discussion

In goats, full immune response expression, seems to be delayed by 6 months i.e. 12 months versus 6 months in goat to sheep [22]. Immune differences in expression between the two hosts are also been documented [4, 23]. It is also assumed that goats tends to accumulate parasites more than sheep. Because of goats weak recognition, and expulsion systems, larval reduction and expulsion of larval or/and adult worms are rarely observed [11, 24]. DTH infections under ordinary circumstances could be reduced as a result in changes to; (i) helminthes resistance by developing an immune response (ii) infective contact especially by avoidance feeding pattern of goats; and (iii) self-medication as results of alleviating worm challenges [4].

In this modern era, helminth's genomics and proteomics understanding tend to provide dependable evidences on presence of large number of immunomodulatory products. These are abridged in number of articles. We can group them in immunological phases;

3.1 Immunological phases

i. initiation,

ii. recognition of antigen and processing,

iii. adaptive immune response,

iv. cellular effector factor responses, and lastly,

v. coagulation, healing, or remodeling.

3.2 Parasite immune-modulators

In each phase, parasite immunomodulators acts specific phase [14, 25]. Immune responses, against most DTHs, are initiated by vulnerability signals generated by initial indicator molecule. The pivotal role of pathogen- or damage-associated molecules patterns (PAMPs and DAMPs respectively) are recognized through receptors on myeloid cells [14]. These chemical identities are acknowledged directly to the physical presence of helminthes in goats' gut [25]. The parasitic induction by DAMPs and PAMPs signals are presented in following figure [14].

Helminthes and some of its products, released by them, can damage the epithelial layer, resulting in the release of damage associated molecular patterns (DAMPs) and which ingresses in the intestine. DAMPs and pathogen associated molecular patterns (PAMPs) can be sensed by receptors that are present on dendritic cells (DCs) and macrophages (Mϕ) [14, 26]. The attachment signals are followed by activation, and antigen presentation to appropriate lymphoid cells [27, 28]. These extracytosolic signals, transmitted as cytokines, influence the central hub of innate lymphoid cells 2 (ILC 2) bundle that stimulates IL 25, IL 33, and thymic stromal lymphopoietin (TSLP)—protein that enhances the maturation of myeloid (CD 11c) dendritic cells. The release of ILC 2 consequential provide signals to type 2 cytokines that amplifies immune type 2 reaction. This aids in the initiation and amplification of the type 2 immune response [29].

4. Innate lymphoid cells (ILCs)

Since last a few years, new players have emerged in cell activation and sustaining an immune response to helminthes infection. The innate lymphoid cells (ILCs) bundles are collection of assorted population that are discovered recently. These collections does not initially express any specific antigen on receptors [30]. These lymphoid cells believed to orchestrate adaptive immune system, type-2 innate lymphoid cells (ILC 2), activities were able to demarcating ILC 2 functions, especially in helminth infection [31] (**Figure 3**).

This all came into the picture, after the discovery, within the T- and B-cell-deficient mice. Functional analysis of ILC 2 and TH 2 cells showed that they share common roles. To secrete rapidly cytokines and in large quantities, these two group of cells coordinate and interact with each other directly [14]. The cells release cytokines (type-2) after spur from Alarmin—IL 25 axis [32, 33]. On the topic, many study reports on origin, differentiation, mobility, functionality, plasticity, and communication skills of these cells within the immune system [33]. The ILC family includes ILC 1, ILC 2 and ILC 3 [30]. These clusters originate from common innate lymphoid progenitors (CILPs). CILPs cells transform into differentiate into ILC precursors (ILCPs) [34, 35]. The system polarize into three different innate lymphoid cell populations; ILC 1 via expression of Tbx 21/T-bet [36, 37] that predominantly express IFN-γ The ILC 2 bundle is acted upon by GATA 3 and RORα factors. The RORα is an absolute requirement for the development of ILC 2 bundle which expresses IL 5 and IL 13 [27, 31]. Literature citations show that development of ILC 2 is rather primitive.

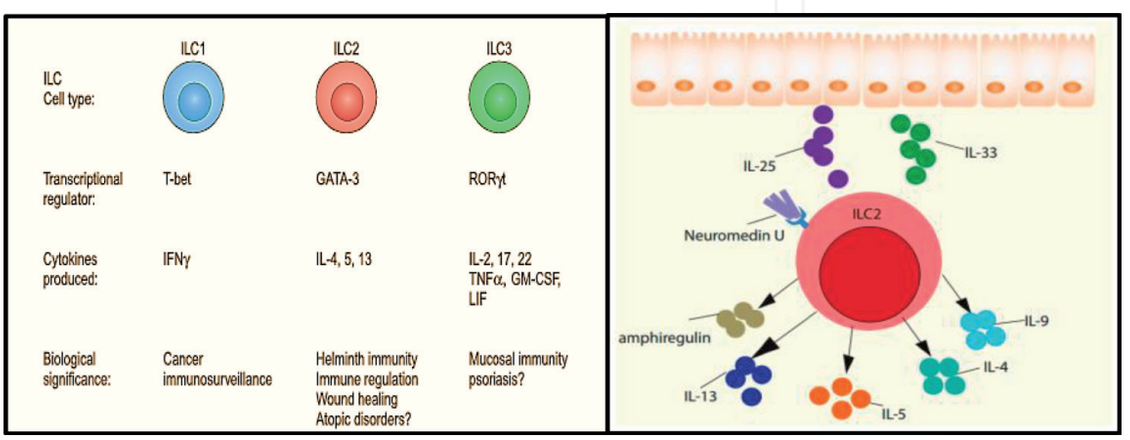


Figure 3.
Types of ILC and activation of ILC 2 and release of various interleukins [30, 31].

Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets [38]. The last but not least, ILC 3 differentiate with RORγt expression that provide stimulus by cytokine signals through IL 22 and/or IL 17 [33].

ILC 2 is considered as tissue-resident in the gut. On infection with helminthes, expansion occurs at the location of mucosal place [39]. ILC 2 s were first discovered in gastrointestinal (GI) nematode infection models. These bundle of cells modulate immune system at tissue mucosal sites; i.e. lung, small intestine, colon, and MLN. These cells are also present in the bone marrow, spleen, liver, kidney, and adipocyte tissue [38]. When parasites drive the immune reaction to produce goblet cell hyperplasia, mucus production, smooth muscle hypercontractility and ultimately worm expulsion [31] (**Figure 4**).

ILC 2 group, important in helminth infection, is further categorized into (i) natural and inflammatory (ii) cytokines responsive groups [41]. This classification is recently challenged by Germain and colleagues [42]. This model is further refined

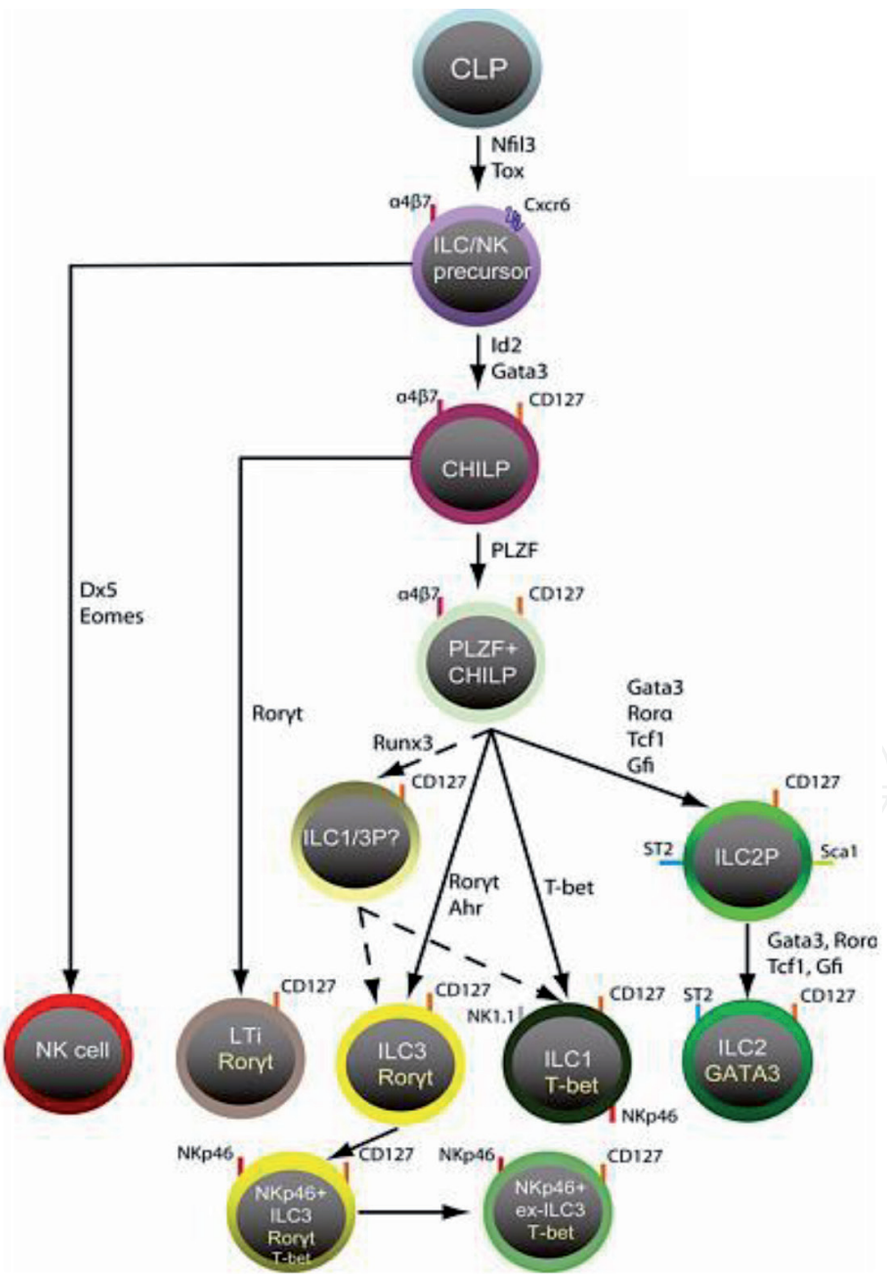


Figure 4.
Cell signalling of transformation of Immune cells [40].

with tissue-resident lymphocytes across innate and adaptive ancestries with migratory capabilities [43].

Unlike T cells, ILC 2 bank on the activation on cytokines. ILC 2 bundle are a critical innate source of type 2 cytokines. As discussed above, helminth infections excite type-2 adaptive responses which results in a SOS on the immune evasion strategy [44]. This circumvention quality was identified over decades ago. Helminthes evolved to modulate their host's immune responses also [43]. This down-regulation of immune response outcomes in asymptomatic animals that maintains the life cycle of the helminthes within them [45]. The transducer signals initiate secretion of moderate magnitudes of IL 5 and IL 13. In the second activation signal, IL 4, IL 9, granulocyte macrophage-colony stimulating factor (GM-CSF), and Amphiregulin (protein produced after stimulus by IL 33 on the tissue damage of intestine) are produced. These cytokines potently induce Mϕ migration inhibitory factor (MIF), rapid production of eosinophils [46]. ILC 2 clusters tend to be extremely receptive to Alarmins—host biomolecules that cause noninfectious inflammatory response [33, 46].

4.1 T_H 2 type immune responses

The T_H 2 type immune responses comprises with three independent modules; inflammation, wound repair, and resistance to helminthes [47]. The T_H type 2 specific immunity against helminthes are delimited by CD4 TH 2 cells that create signal transduction to produce interleukin (IL) 4, IL 5, IL 9, IL 10, IL 13, Immunoglobulin (Ig) E and chemokine ligand CCL 11 [48] (**Figure 5**).

Helminthes, especially nematodes, developed numerous workings that restrain host to act on them. This provoke instigation to innate and adaptive regulatory cells, inflammatory cytokines and inhibitory antibodies [50]. One of studied example, is the chronic infection of *H. polygyrus*, which showed that there is very little expansion of ILC 2 pool in nearby mesenteric lymph nodes [51, 52]. Probable enlightenment on the issue showed that such infections validate with the release of host derived IL 1β which take a check on for the production of IL 25. This IL 25 acts in return on the ILC 2 cluster [27, 53]. ILC 2 cluster are identified by their expression of IL 2, IL 25, IL 33 and IL 33 receptor (IL 33R) with activation of p38 MAPK that phosphorylates GATA 3 [54]. These factors in return reduce the Ig E, as well as IL 4 and IL 5. They recruit, migrate and infiltrate with these activated eosinophils, basophils and mast cells [33].

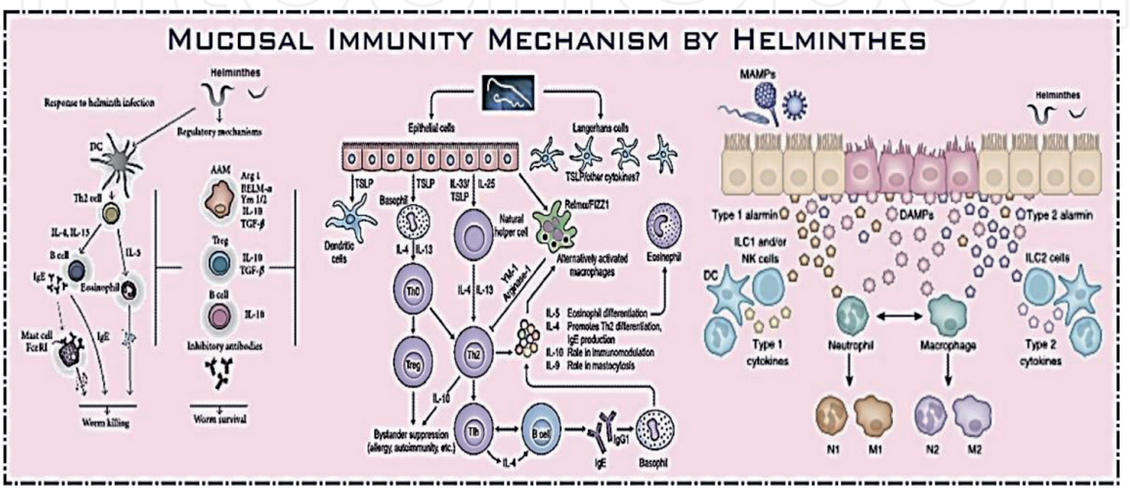


Figure 5.
Cell signaling of transformation of immune cells [49].

5. Dendritic cell and subsets

The dendritic cells (DCs) are a heterogeneous population of immune cells that have specialized functions. All types of DCs are principally regulated by well conserved, various transcriptional factors. These cells are divided into conventional or classical DC (cDC) and the plasmacytoid DC (pDC) [55]. The plasmacytoid DC acquired function to intuiting the nucleic acids and in response producing large quantities of type 1Interferon (IFN) [40, 56]. The other, cDCs, tend to be more active in specialized work of antigen presentation, and later activation of primary T cells. Today, we can further subdivide cDC into murine CD8a/CD103 and CD11b cells [57]. Transcriptomic studies represent a powerful tool to determine the phylogenetic relationship between different cell types of the immune system, including DC [58]. Analysis between goats/murine and human DC subsets differentiating into MF from DC and classifying DC subsets [59]. Dendritic cells (DCs), in animals, in immune competent system accredited to helminthes infection as extensively reconnoitered in past. These infections tend to incline and persuade T_H 2 type cells to respond effectively. However, this recognition of helminthes is not yet fully resolved or understood [60]. In the first set of cells are those which specializes in presentation of antigens to CD 8 T cells. These cells prompt to mucosal immunity through T_H 1 cells. Whereas the other, murine CD 11b cells, cooperate with both CD 4 and CD 8 cells for its subset activation. These cells provoke specialized T_H 17 cells through the stimulus of Interleukin (IL)—17 secretion [59]. The IL 17 activities setup all the framework for type-2 cytokines, and mesenteric lymphoid clusters activation [61]. These neo innate lymphocyte clusters, found confined to differing tissues, which is part and parcel of type 2 cytokines albeit to monikers as "nuocytes" or "natural helper cells" [62]. This stimulation geared up for the first response to the immune challenges caused by helminth infections [63].

5.1 Intestinal DCs and macrophage subsets

Dendritic cells (DCs) subsets, which differentiated from ILC bundle, perform compounded roles in final outcome in the immune responses. In the gut, DCs handshake many exogenous antigenic pathogen to prevent infections [64]. The intestine DCs and amended Mϕ appears to be indispensable in the instigation of active immunity and homeostasis in the gut. These cells have unique ability to rove through the goats mesenteric lymph nodes (MLNs) to perform key start of naïve T cells priming for adaptive immune response [65]. These intestinal DCs and Mϕs within the lamina propria perform vital steps in the initiation, development and regulation of specific intestinal immunity [66]. Most naïve T cells mature up in peripheral lymphoid organs. These cells get expression activation through gut-associated lymphoid tissues (GALTs). In goats, Peyer's patches and mesenteric lymph nodes (MLNs) act as hub of transformation of the CD 4 T and CD $8_{\alpha\beta}$ T cells which in turn prime the antigen-presenting cells (APCs) [67]. The lymphoid associated organs attain the ability to transfer to intestinal area with specific gut homing molecule, integrin α4β7, by its upregulation and others [68].

6. Helminthes and dendritic cells

In the small intestine, Lamina propria harbor large number of DCs. All of these intestinal DC subsets are well studied and documented. Of these both highly expressed $CD11_c$ and Major Histocompatibility Complex (MHC) class II cells are of real importance [69]. Phagocytic group of cells in Lamina propria comes from different lineage and perform diverse functions [70]. Relocation of these DCs tend

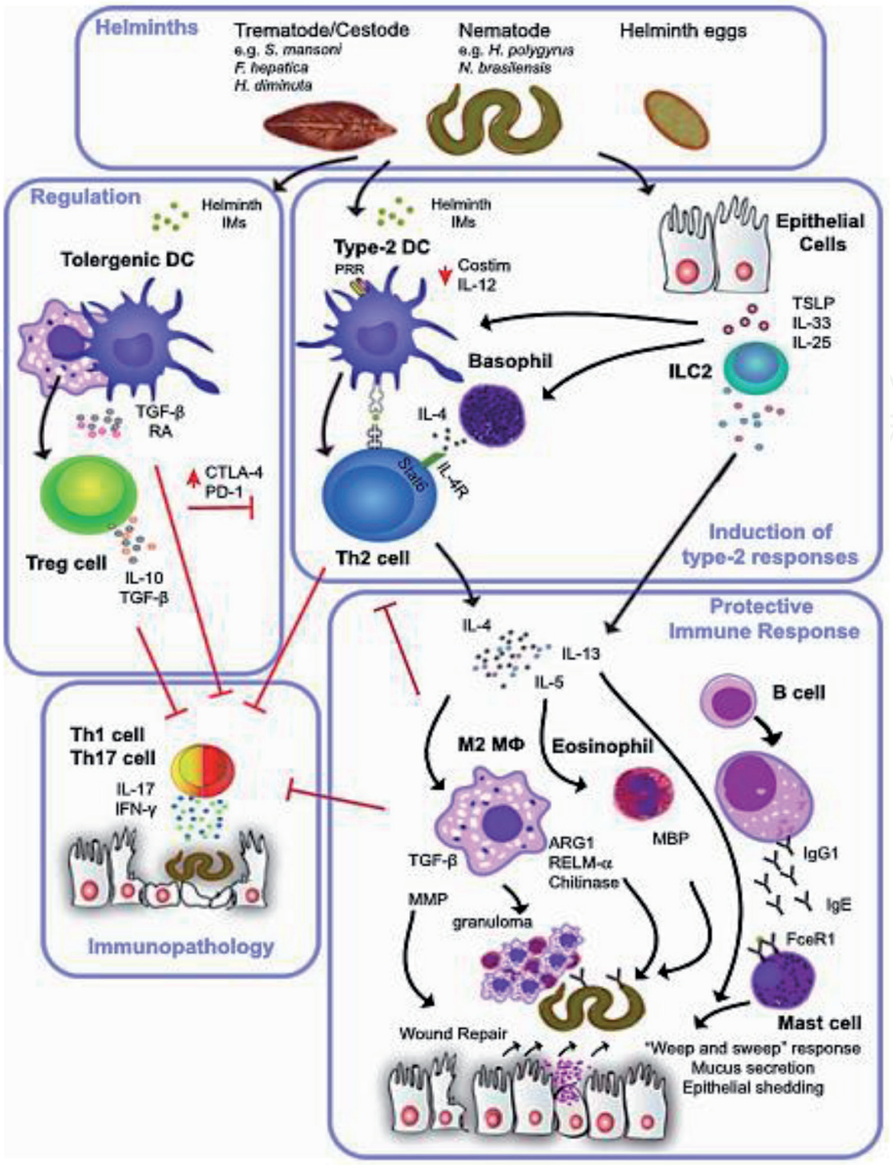
to be tightly regulated by one gene product, CCR7. Expression levels of this gene largely control non-migratory and migratory scenarios [43, 71]. In payer patches, CD103, $CD11_b$ expressing and non-expressing DCs are well studied that induces lymphocytes [72]. Many T cell receptor (TLR) expressing DCs also induce the production of Immunoglobulin (Ig) A. On the other hand, pDCs can incite IgA directly and repress inflammatory processes [73].

7. Extra-helminthes immune molecules

Research studies on helminthes immune modulation system is more engrossed to find cytokine activation, release and mechanisms of cytokine-mediated effector functions. This all rely on the first immune recognition, probably PAMPs and DAMPs, and message of early immune response activation or even suppression. Later this signal is converted to sustained and regulatory immune response [14]. It is observed that in the early phase, limited inflammation occurs in the invading tissues which is overlooked by immunoregulatory milieu to evade, and survive [74]. One of the tool these invading parasites is are; (i) apoptotic processes against immune cells [75], (ii) manipulation of Pattern Recognition Receptors (PRRs), (iii) lowering of T_H 1/T_H 2 cells and (iv) associated cytokines activation [76]. Recently many goat helminthes shown to ubiquitous cog with the release of endocytologic extracellular vesicles (EV) on to cytoplasmic membrane in the intestinal Lamina propria. EVs are vesicles slashed out by different categories of cells which plays role in modulation of immune response to helminthic pathogenesis [77]. Depending on their sizes and origin, these are classified into three types; Microvesicles, Exosomes, and Apoptotic bodies. The exosomes range in size from 30 to 100 nm in diameter that are released by the cells. Microvesicles, however, also called ectosomes—shed 100–1000 nm vesicles or microparticles. Lastly apoptotic bodies are just 2–4 μm in size that are released by dying cells [78].

7.1 Chemical analysis of EVs

The chemical analysis of EVs revealed that they contain soluble proteins, lipids, and carbohydrates with immunomodulatory action [79]. Helminthes counter with a palette of protein modulators, from protease inhibitors to receptor ligands that target these pathways [14]. The list of these immunomodulatory molecules are increasing over the last decade [80]. Many parasites release exosome and/or microvesicles. These vesicles play a cornerstone to the downstream communication into the immune system [81]. These vesicles actively induce IL 33 which binds to IL 33R that pledges an allergic reaction. These EVs or exosomes also inhibits activates ILC 2 and eosinophils [77]. Recent investigation on EVs of *H. polygyrus* showed that they suppress receptor for the Alarmin—cytokine IL-33 in ILC 2 [74]. The internalization of EVs causes down regulation of IL 33 and type 1 and type 2 immune cytokines; IL 6 and TNF, and Ym1 and RELMa [81]. Several documents demonstrate that exosomes promote TH 2 slanting towards the activation of DCs and T cells during infection and vaccine development (**Figure 6**) [82]. Recently, evidences are brought forward to the notion that EVs are secreted by both the parasite and the host [80]. Interestingly, it is suggested that there helminth plagiaristic EVs structures could also be used in the inflammation regulation, especially in allergic, autoimmune, and metabolic disorders regulated by miRNA [83, 84]. Helminth immune modulation has some beneficial effects as allergies, and inflammatory and autoimmune diseases which are less common in populations infected with helminthes. A large body of literature provide reasonable evidences on mechanism of immunomodulation that arise from the helminth infections [85].



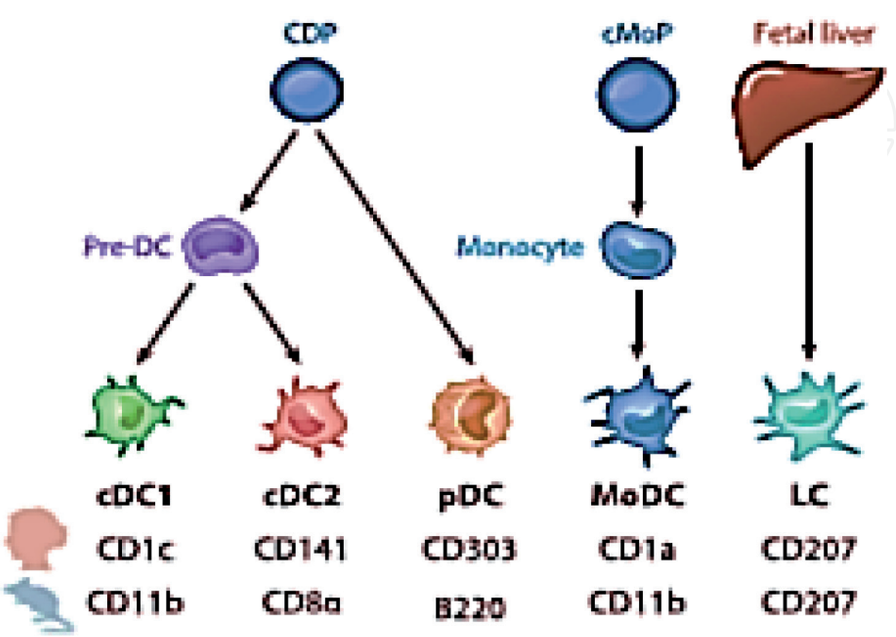


Figure 6.
Types of dendritic cells.

In goats, a definite systematic immune regulations is contemporaneous placed in various world breeds of goats [25]. In sheep, explorative investigates lead us to draw near perfect immune mechanisms followed after the helminth infections and vaccination [86]. It is to remember that helminthes when infect goats, they are not recognize merely whole organism, rather it is a combination of small amino acid sequence derived from PAMPs and DAMPs attached to the cellular peptide-MHC (pMHC) within the groove of MHC molecule [87]. The bound peptide (8–11 amino acids for MHC I and 13–22 amino acid for MHC II) is presented to antigen-presenting cells (APC) through groove—exposed motif (GEM) [45]. The induction of systemic immune responses following parenteral immunization occurs in similar ways in many species including mice, humans, and small ruminants [88].

7.2 Mucosal immunity

The development of effective mucosal immune responses by way of vaccination is considered important because mucosal immunity is able to prevent early establishment of the pathogen and hence could at least theoretically prevent infection at an earlier (less damaging) time point. Thus, vaccines targeting mucosal sites have been in development for a considerable amount of time [88]. The primary protective surface at mucosal sites is the secretion of mucus form gastrointestinal lining. Mucus is a dynamic multimolecular matrix built on polymeric, gel-forming glycoproteins (mucins), with different mucins dominating the barrier at different mucosal sites [89]. At mucosal sites, specialized epithelial cells such as goblet cells secrete gel forming mucins. Upon infection, these cells undergo hyperplasia and increase mucin production, which expands the secreted mucus barrier and provides protection against multiple pathogens [90, 91]. The formation of mucus layer also add on; (a) antimicrobial molecules (e.g., IgA, lysozyme, defensins), (b) immunomodulatory molecules (e.g., cytokines, secretoglobins), (c) repair molecules (e.g., trefoil proteins) [29]. In mice model, the mucin producing Muc 2 are major producer of gel like mucus formation that creates a barrier against contact to the lining in the gastrointestinal tract. This mechanism also provide in return helminthic worms modulating antigen and tolerance [92]. Off the subsets, Muc5ac cells are specifically upregulated after worm infection that also influences expulsion of worm [93, 94]. The sheep model in studying immune mechanisms, with special reference to mucosal immunity, by using nasal vaccines and delivery systems suggested specifically the distribution of the antigen with in the lymph nodes, processing, induction and drainage [88]. Innate lymphoid bundle cells (ILC 2) and T_H 2, as discussed above, share common feature of secretion of IL 13 with differential kinetics for each type [29] (**Figure** 7).

7.3 T cell subsets

T cells as well B cells tend to form two major components within the adaptive immune system. The initial T cell development starts in the bone marrow from hematopoietic stem cells (HSCs). The T cell predecessors pass through to the thymus, from where it gets acronym. The differentiation steps provide ultimately culminate into various mature T cell subsets. The whole process is summarized in **Figure 1** [95]. T-cell development/maturation is very much dependent on their presence within the thymus. In mice, absence/removal of it generates severely impaired T cell development [96]. The differentiations and developments of, especially, T cells produces T cells, B cells, natural killer (NK) cells, or dendritic cells (DCs). However, further stoppage within the thymus, further differentiate into these

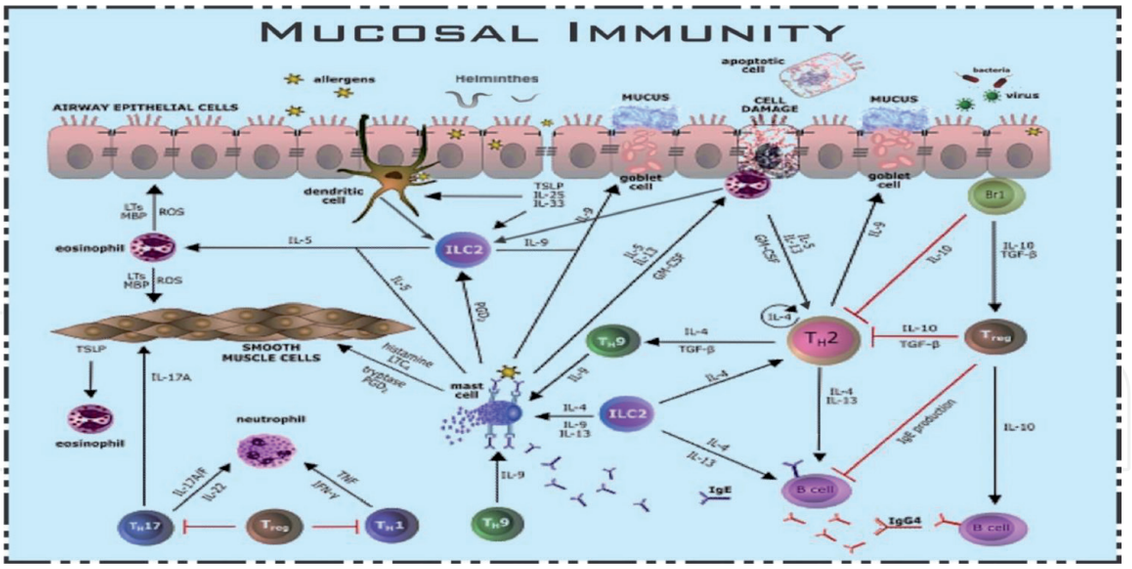


Figure 7.
Cell signaling network through mucosal immunity.

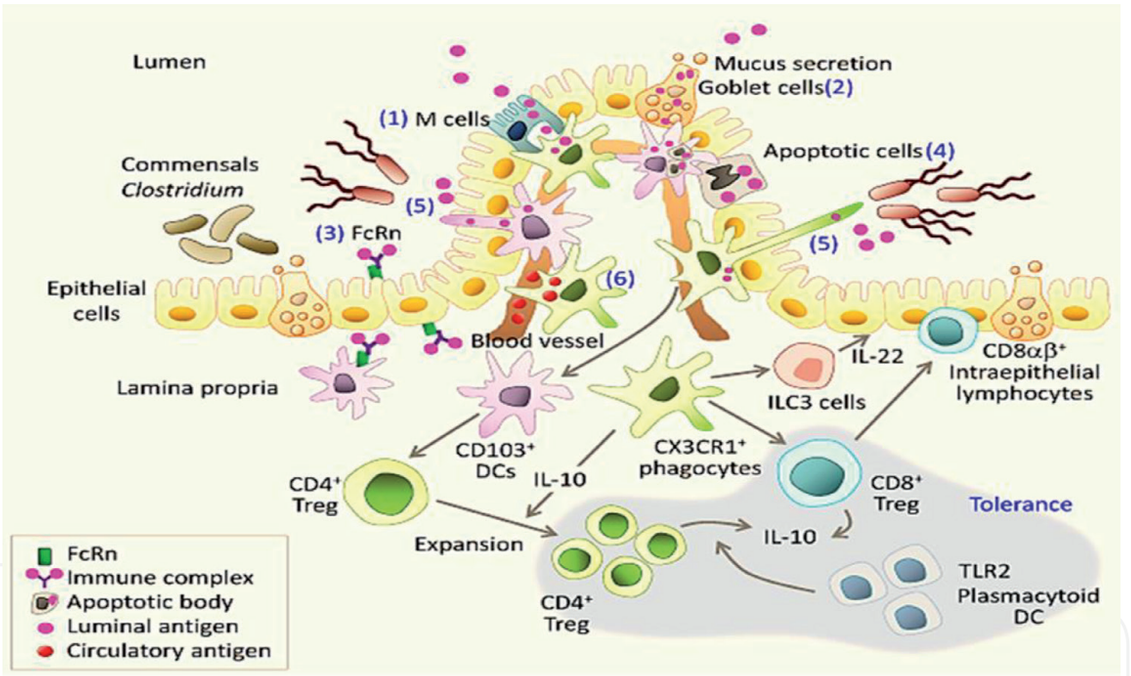


Figure 8.
Microenvironment in the Helminth infection.

subsets the maturation of these subsets i.e. B cell, NK cell, or DC differentiation occurs in bone marrow and fetal liver (Rich eBook).

7.4 Formulation of immune response

In the formulation of immune response, Treg cells a produce homeostasis and secondly the autoimmune suppression. A growing body of evidence suggests that the Treg cell repertoire contains organ-specific/tissue specific Treg cells. Treg cell share specificities in lymph nodes throughout the body, suggesting that the anatomical distribution of Treg cells is shaped by the presentation of regional organ-specific antigens [97]. On the other hand, the Macrophages (Mϕ) show profound differences with various profiles. Under the influence of an alternative phenotype

(also labeled M2 cells) which occurred by the presence of helminth infection. This is driven by type 2 cytokines IL 4 and IL 13 cytokines (**Figure 3**). Ongoing research divided these Mϕ by gene expression, metabolism, and function differences into classically activated (M1) macrophages. However, M2 macrophages are required in the effective immunity to some parasites (including *H polygyrus*) [15]. The DCs are professional antigen-presenting cells (APCs) that play an essential role in presenting antigen to T cells to initiate immune responses. Although the role of DCs in inducing T_H 1, T_H 17, and Treg responses is well established. Often overshadowed by their T-cell counterparts, regulatory B (Breg) cells are also crucially important in control of the immune response during helminth infection [15] (**Figure 8**).

These DCs can also patrol among enterocytes while extending dendrites towards the lumen [16]. Treg cell population by producing IL-10 to harness immune tolerance [98]. CX3CR1+ phagocytic cells can capture Salmonella by extending dendrites across epithelium in a CX3CR1-dependent manner [99]. Antigens captured by CX3CR1+ phagocytic cells can be transferred through gap junctions to CD103+ DCs in the lamina propria to establish oral tolerance [100]. In addition to luminal antigen, lamina propria CX3CR1+ cells facilitate the surveillance of circulatory antigens from blood vessels [73].

8. Host-parasite interaction

Almost all animals get gastrointestinal infection (GI) by helminthes in their lifetime. Though all parasite (Helminthes) species share a very similar general morphology and they undergo into four molts reforms during their development period [101]. Each of the species shares dioeciously life spans that could be weeks to years. These worms are investigated because they threaten animal as well to the human health [102]. Nearly all helminthes invade tissues and install an immunomodulatory surrounding for their survival especially taking care of Treg cells [103]. Recently cites articles suggest that both, worms and host, evolved to get reciprocal immune related benefits during the disorders with some clinical outcomes. Numerous studies suggest that immune response appears to be imprisoned that is even extended to expansion of Treg cells [103]. As a consequent a melioration of type 2 immune response that resulted in chronicity [103]. Many findings, however, chronic helminth infection are still poorly understood. These parasites are also important as a model where they create constant, foremost challenge to host immune system [101]. Many of aspects, especially regulation of chronic GI infection, remain to be defined. It is believed that during the evolutionary processes they exclusive adapted to such avoidance to host defenses [104]. These masterful adaptations enable them to remodulate host immune response [105]. It may well be the evolutionary mechanisms that exclusively down regulates early expansion of ILC 2. This is seen in *Heligmosomoides polygyrus* system where IL 1β shows to down regulate early ILC 2 responses in mice [106]. However, this is not true for another parasitic *Trichuris muris* infection where IL 1β null mice [107]. This depression in the levels of IL 1β provokes type 2 protective immune responses, and leads to worm expulsion [53]. The helminthes in the GI tract interact with the mucus layer and many a times pass through into the epithelial layer and reproduce at the site [108]. One of the interaction of worms to intestinal mucosal barrier and hyperplasia, secretion large mucin forming a layer. The mucus layer is a highly hydrated gel mucins. These are largely high molecular weight glycosylated glycoproteins secreted by goblet cells (GCs). The initial also interact with antimicrobial compounds, commensal metabolites and finally antibodies. Like in mouse as well as in humans, MUC 2 cells produces to mucus layer as predominantly part first line of innate immune response [109].

Mucin production is synchronized by many immune type 2 cytokines. As discussed above, IL 4 and IL 13, plays key role in proliferation and differentiation of these GCs [101]. As the intestinal infection ensues it initiates worm expulsion seen for many helminthes [110]. This expulsion is influenced by the presence of CD 4 T_H 2 cells which are controlled by IL 13 secretion [27]. In the knock down mutant studies in mouse showed that MUC 2, regulated by IL 13, led to defective delay in worm expulsion [101]. The, above described, incitation of type 2 immunity releases IL 4, IL 5, IL 9 and IL 13. Several other immune and nonimmune cell activators also participates in the web of effector mechanisms that also sways to parasite expulsion [111]. The commencement of the immune response by TH 2 cell trails through ILC 2 and subsets of dendritic cells. The sensed and trigger signals, however, of PAMP and DAMP results in the activation of different subsets of ILC 2 bundle, dendritic cells, various types of T cell types, basophils and nonimmune intestinal epithelial cells (IEC) against intestinal helminthes. The heterogeneous intestinal epithelium contains seven different cells that can sense helminth invasion into the epithelial cells to initiate T_H 2 cell mediated immunity [103].

9. Secretory IgA and intestinal DCs

Total serum protein in goats is in the range 6.75–7.53 g/dL [112, 113]. In the group of proteins, fibrinogen levels in goats fall between 0.1 and 0.4 g/dL, which are less compared to cows. In some instances hyperfibrinogenemia occurs with neutrophilia after inflammatory responses. In goats, however, maximum plasma fibrinogen levels are 1.1 g/dL during inflammation [114]. In the protein gamma globulins share considerably. In goat, there are three main immunoglobulins; Ig G, Ig A, and Ig M. In caprine, like in cattle and sheep, there are further two distinct IgG subclasses, IgG_1 and IgG_2 [115]. At the birth, IgG_1 is present in the colostrum. Moreover, IgG_2 is preferentially transported to mammary glands from serum as IgG_1 share high affinity to IgG_1 for Fc receptors on mammary epithelial cells [116]. The goat IgG_1 is the subclass that is predominant circulating antibody

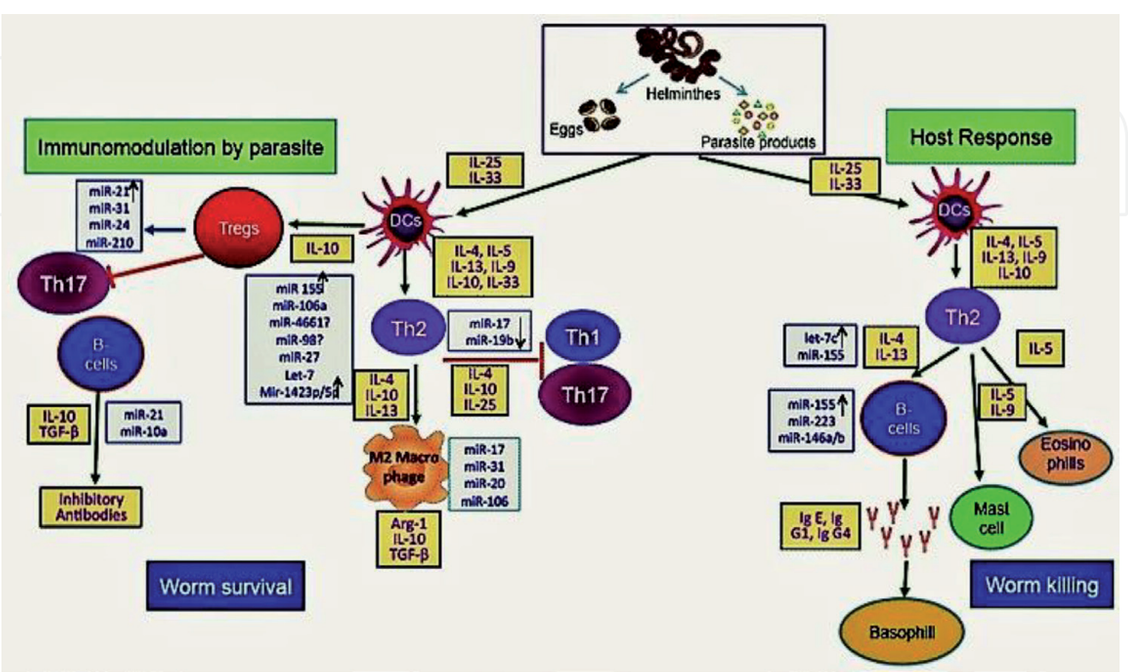


Figure 9.
miRNA regulation of immune response against Helminth infection.

which is produced in response to any infection which later isotopically switch to Ig E functions [117]. Locally generated IgG_1 is also detected after arthritis encephalitis (CAE) virus infection in the synovial fluid [118]. Very few work has been done for caprine IgM concentrations and activities. All the ruminant species observe little structural and functional differences [119]. Caprine IgA, on the other hand, is detectable from serum, colostrum, milk, saliva, and urine. IgA is the primary immunoglobulin present in mucosal surfaces. The secretory element to IgA could be found in either free-state or bound to IgA molecule. The serum very small amount of IgA is linked to secretory component [120]. Goat mucosal immune system produces sIgA by antibody producing cells differentiated from activated B cells. Immunoglobulin class switch do occur from IgA in gut-associated lymphoid (GAL) in Peyer's patches, MLNs, and ILFs within the lamina propria [28, 121]. The humoral immunoglobulin isotype switch occurs through intestinal pDCs, T cell-independent manner and B cell-activating factors (BAFFs) and A proliferation-inducing ligand (APRIL) proliferation inducing ligand [73]. Like in all ruminants, including goats, IgE typically associated to its biologic activities. Today IgE is accepted as useful marker in identifying different phases of parasites and parasite resistance. Nucleic acid sequencing in caprine IgE DNA is part of the overall effort [110, 122]. Goat's complement system is provided with limited concentrations [123]. Dynamic studies showed that in less than 6 month old young and adult indicate significant hemolytic, conglutinating, and bactericidal complement activities [124] (**Figure 9**).

10. miRNA regulation in goat immune system

Recent literature cites of the immune cells that are communicated through from one cell to other by transferring regulatory RNAs, microRNAs in particular. Many studies pin point that some sort of functional, regulatory extracellular RNAs plays a key role in cell-to-cell communication in various cellular processes [125]. MicroRNAs (miRNAs) are group of short RNA non coding sequences that are highly conserved between different eukaryotic species [126]. These are ~19–28 nucleotides long sequences that regulate(s) gene expression [127, 128]. miRNAs are particularly important in the cellular function that show time dependent responses [129]. miRNA literature show that they partake a mesmerizing role in both immune system and as an immune system [130]. These small RNAs lead to vertebrates transcriptional silences like a rheostat that act to fine tune (rather than complete shut-off) of translational products. The miRNA targeting could result in 3-fold decrease of mRNA transcripts [131]. In many studies, till now, more than 60% miRNA expression profiles are developed and tested in variety of tissues from livestock. These profiling post transcriptional regulate gene expression in several cellular processes such as differentiation, and transformation processes in cell cycle through signal transduction [127, 132]. miRNA molecules could broadly act as regulators on shorter time scale on protein transcriptional repressors that effect inflammation. They can also show quicker results without engaging translational or translocational machinery within the nucleus and controlling regulators. One example to this is the miR 155 regulation [129, 133]. Together with these options opens up many avenues that provide novel and exciting products in therapeutic as well as in clinical use, specifically for immunity and inflammation Today miRNA functionality can be dissected in leukocyte differentiation, innate signaling, and T_H cell biology [132]. *In-silico* studies using various tools on miRNAs on computation or experiments gathered about 35 Helminthes (11 Trematodes, 8 Cestodes, and 16 Nematodes, and two plant origin parasitic Nematodes). These analysis show that greater than 620

plus pre-miRNAs that are listed in miRBase of parasitic origin. Interestingly, the first miRNA was discovered in *C. elegans*, a nematode [133]. All known parasite miRNA database entries are analogous to miR database. The emerging, neglected disease of *Schistosoma*, a trematode, is one of the iRNA models in the whole family [134]. The miR database showed that there are 79 and 225 mature miRNAs associated to *S. japonicum* and *S. mansoni* respectively. These findings indicates that not only large number of variations do occur within the helminthes, but male and female worms also show differences. This also give insight to the role in morphogenesis, development and reproduction [135]. A similar picture arises from Next Generation Sequencing (NGS) and bioinformatic analysis and experimentation with stem-loop qRT-PCR identifies 13 species specific miRs in two species *Fasciola hepatica* and *F. gigantica* [134]. Studies on infection, more than 130 miRNA (analogy to other parasitic miRNA), are seen to flocculate in expression profile [135, 136]. It is shown at many instances that miR 155, miR 223, miR 146 are negative, suppressors of cytokine in a regulatory loop. In other studies, miR 155 is also interactive to transcriptional factor cMaf and tempers with TH 2 within the CD 4 group. In another analogy to a mouse model, same miRNA 34c, miR, miR199, miR 134, miR 223, and miR 214 are shown to effect 220 miRNA parasitic immune response silhouette [133, 137]. The powerful approaches of bioinformatics extrapolations along with stem-loop real-time PCR analysis on the *C. sinensis* showed that there are a total of 62,512 conserved miRNA sequences which includes six novel identified miRNA [138]. Pak and coworkers [135] demonstrated that there is an upregulation miR 16-2, miR 93, miR 95, miR 153, miR195, miR 199a-3p, and silences with miR let7a, let 7i, and miR 124a in the presence of EVs of *C. sinensis* [133, 139].

10.1 miRNA regulation of T cells

As a critical role of miRNA post transcriptional regulation in transformation within immune cells show that these tiny molecules can reduce the expression of various genes by 3 orders of magnitude during maturation [140]. Studies showed that different miRNAs are involved in the thymocytes development by Dicer or Drosha knockouts experiments. Obstruction in the process consequential drop of mature $T_{\alpha\beta}$ and natural killer T (NKT) cells [141]. In animals' helminthic studies, absence or presence of miR 155, showed that it can effect TH 2 differentiation involving apoptotic processes [131]. miRNA machinery knockout experiments demonstrate that some of the miRNA are of absolute requirement for Thymic development and peripheral function of nTreg cells. However, dicer knockout of Fox P3 cells consequences to nTreg cells without oppressive role. Treg cells can also transform into T follicular helper cells that resulted in loss of immunomodulation and B cell activation in this scenario miR 155 is a regulator of nTreg cells. It should be remembered that miR 155 is expressed in all adaptive immune cells [142]. The expression and formation of active miR 181a is found to be tightly regulated intrathymic T cell development. The activities modulates the T cell antigen receptor (TCR) retort the down regulation through phosphatases which plays pivotal role in reducing TCR cell signaling. Thus the activities of miR 181a acts to modulates of TCR sensitivity towards T cell development in the lymphoid organ [131]. Blockage with antagomir (oligonucleotide) to miR 126 reduces the differentiation of TH 2 which are linked to helminthic pathogenesis during innate immune system activation. During this impasse, T_H 17 cells regulate another miR 326 within their reach by up regulation [143]. These cells are differentiated and regulated by cytokine IL 23 [144]. It is shown that miR 17 polarizes then T_H 2 cells, required in type 2 immune response to helminthes infection [141]. Mature T_H cells are further influenced by miR 182 in response to IL 2 cytokine synthesis. This regulation is

post transcriptionally controlled with transcriptional factor Foxo 1 [145]. The ILC 2 bundle of cells are differentiated by GATA 3 factor, as discussed above. This transcriptional factor induces T_H 2 differentiation and produces larger quantities of IL 4, IL-5, and IL-10 *in vivo* and IL 13 [31, 141]. It is documented that miR 126 regulation effects TH 2 polarization. In mice, an activator of transcription is targeted through POU 2F3. Furthermore, PU-1 significantly inhibits specific binding GATA 3 factor. Another molecule of interest is miR 126 where *in vivo* studies proved that it reduces T_H 2 cells to specifically allergy promoting dust mite antigens [146]. miRNA machinery knockout experiments demonstrate that some of the miRNA are of absolute requirement for thymic development and peripheral function of nTreg cells. However, dicer knockout of Fox P3 cells consequence to nTreg cells but without oppressive role. Treg cells can also transform into T follicular helper cells that resulted in loss of immunomodulation and B cell activation in this scenario miR 155 is a regulator of nTreg cells. The suppressive part of miRNAs by the Treg cells can act on two points; (i) Treg regulating themselves, (ii) modified response of target cells on Treg cells [147].

10.2 miRNA regulation of B cells

Like T cell lineage, B cells also are tangled up with various miRNA classes that regulate their differentiation and development within the bone marrow. The miR 181 overexpression in hematopoietic bone marrow increase in the fraction of B cell subtypes. Similarly miR 150 effect the B cell development at pro- and pre-B cell transformation due the apoptosis. Knockdown miR 155 mice reveals skewed CD 4 T cell polarization in the T_H 2 subset [141]. B cell studies show that two miRNA, miR 155-5p and miR 155-3p, are expressed solely in these cells [148]. These miRNAs are positioned in Integration Cluster gene (BIC) area that positively prompt to various stimuli within the immune system [149]. Germline studies on miR-155 showed that its deletion induces reduction of B cell germinal centers [131, 150]. In mice, upregulation of miR 34a in the progenitor cells are acknowledged. Constitutively miR 34a expressed in B cell studies conclude that it block differentiation of pro-B to its next stage of pro-B cell and to mature B cell. The disparity occurs through Foxp 1 [148, 150]. Number of expression profile studies show that dysregulation is found for miR 182, miR 96, miR 183, miR 31 and miR 155 that effects B- and T-cells. Recent finding on miR 150, miR 127 and miR 379 also showed that there upregulation effects splenic maturation processes. The miR 150 levels are predominantly present in both B-cells and T-cells not on to their progenitors. On the other hand, miR 15 activities that it correlates to autoantibody production [150]. Another regulator The miR 17, encode several miRNAs from same transcript, also show that it negatively influences on pro- and pre-B transition through a blockage of BIM accumulation [131, 150]. Another protein, BMI 1—a ring finger structure, also promotes differentiation of TH 2 in a mouse model that in return stabilizes GATA 3 protein for transcription by protecting it from ubiquitination [141].

10.3 miRNA regulation of cell cycle

Numerous citations show that cell cycle of T cells are directly regulated by miRNAs profile. The regulation is associated cell cycle check points through Cyclin T1 levels in Mϕ. It is documented that miR 182, as shown above, functions on expression of generalized transcriptional regulator, FoxO 1. This control regulates CD 4 T cell expansion with Cdk inhibitor, $p27^{Kip1}$. Negative feedback on FoxO 1 is accomplish by miR 182. These signals activate IL 2. This induction results in T_H 1, T_H 2, T_H 17 and naïve CD 4 cells expansion. Studies *in vitro* and *in vivo* showed that in a feedback loop, down regulation of miR 182 results in stoppage of spreading

out of CD 4 cells [127, 141]. The nearly all vertebrates, immune system evolved itself to a finely fine-tune, an extraordinarily flexible apparatus within the host defense [125]. Besides direct role of various miRNAs, indirect regulation is also well in place in immune system. This is seen for miR 19a, miR 19b in the miR 17 cluster. These two sequence encode deubiquitylation enzyme, CYC D, which blocks NF-κB activities. Its expression results in Cyclin and other growth factors. In a recent documentation that there is a universal reduction of CD 4 T cells which is one of the hallmark of helminthes infection [141, 151].

10.4 Helminth vaccines in focus

Global data on parasitic helminthes speaks loudly of the livestock diseases that affect many area of the world, including Europe. Their infections are related to huge economic losses in loss of fertility, production and body weight [152]. Cumulative responsible statistics show that more than 55% of livestock suffer from these infections outcome. It causes diseases in Europe and cause highly significant losses in productivity and welfare in animals and then in humans and welfare problems globally. Yearly estimates show that in liver fluke (*Fasciola hepatica*) infections up to US $3 billion per annum are lost [153]. Conservative estimates in the United Kingdom show that gastrointestinal (GI) helminthic infections to sheep industry shares losses of more than £84 million per annum [154]. These infections are traditionally controlled by administration of various anthelmintic drugs [155]. Naïve practice resulted in development of resistance to these medicines. Recent documentations for sheep farming, particularly in New Zealand, Australia and Brazil, showed that Multi Drug resistance (MDR) is much elaborative phenomenon worldwide and have upward trend [156]. Development of these vaccines started some 50 years ago. Most helminth component formulating and their administration showed that they effectively interrupt the dynamic morphological and antigenic changes during parasites life cycle of the worms and can be used as controlling tool [157]. Many helminthes share much sophisticated evasive immune mechanism that is discussed already in detail. This quality of worms make them very hard for scientists to move forward to develop efficient vaccine candidates [158]. Many efforts to develop anthelminthic vaccines in livestock started many years back with limited success [159]. As discussed in detail above, elusive behavior of worms does not provide adequate long-lasting protection at all stages of helminthic maturation [160]. Vaccines provide manifold benefits on improving animal health, welfare and control of animal infection. The use of vaccine also addresses resistance to acaricides, antibiotics and anthelminthic medicinal solutions [158].

At present, there tend to be two strategies to effectively develop vaccine; (i) attenuated and (ii) hidden antigen [159].

10.5 Attenuated vaccines

These vaccines are developed and used after irradiating L3 larval stage that prevents development of mature adult worms. This protection could reach up to 98% *in vitro* with two experimental doses. Attenuated larval *Dictyocaulus filaria* (sheep lungworm) name "DIFIL" for *Dictyocaulus filaria* larva is effectively used in India since 1981 [160]. A similar approaches are used to develop other vaccines.

10.6 Hidden antigens vaccines

Helminthic recombinant integral membrane proteins, part of worm gut, that whenever used provoke high degree of immune recognition and type 1 and type 2

immune responses [158]. In these vaccines enhanced innate and adaptive models suggests logical targeting of T_H 2 cells through type 2 arm of immune response. These types will be future vaccines against the helminthes infections [161].

10.7 Helminthes components as vaccines

The extracellular vesicles (EVs) of various helminthes are heterogeneous type of membrane vesicles that are on the loose by different types of infecting organism. The EVs, as described in detail above, contain complex mixture of transcriptomic messages [162] for proteins, lipids, galectins and glycans [163, 164]. EVs are of three categories divided on cell of origin, molecular contents, function, physical characteristics, specific protein markers, and isolation techniques [165]. The immunomodulatory effects of excretory secretory molecules and EVs influences both parasite worm as well as in the host [74]. Studies on these molecules show that this unresolved issue of the formation, packaging, cargo transportation, nature and mechanism of interaction, functional spectrum, docking of molecules and fusion [82, 166]. Efficacious helminth vaccines are developed seldomly with wide contrasting technologies [152]. Following early immunization experiments on sheep showed there is a wide variety of concoctions processes that releases various antigens that act as vaccine formulation [167]. These crude methods of administration provided induced partial protective immunity. One example of H11 protein of *Haemonchus contortus* antigenicity show differential activity of native and recombinant proteins [152]. New vision on the helminth control is formulated to bring new infusion of technology in the helminth research by 2030. The sustainable goals includes; (i) advancement in global diagnostic tools, (ii) innovative vaccine control and breeding methodologies, (iii) anthelmintic with new compounds, (iv) rationalization in integrated future control [168]. Today very few vaccines of helminthic worms are available in veterinary stores. These include nematodes vaccines for cattle lungworm (*Dictyocaulus viviparus*) vaccine (Bovilis® Huskvac, MSD Animal Health), vaccine against the barber's pole worm (*Haemonchus contortus*) in sheep (Barbervax®, Wormvax Australia Pty Ltd.). Scientists are working hard to develop (experimental phase) vaccines against several helminthes species including; *Teladorsagia circumcincta* in sheep, *Ostertagia ostertagi* and *Cooperia oncophora* in cattle, and *Fasciola hepatica* in ruminants. If these promising trials yield fruitful, wider range helminthes vaccines with be shelved in in the future [169]. In Cestodes, two recombinant vaccines are available for *Echinococcus granulosus* in ruminants (Providean HidatilEG95®, Tecnovax) and for *Taenia solium* in pigs (Cysvax®) are marketed. Rapid progress in the domain of proteomics and glycomics, it seems that in near future more and more synthetic vaccines will be solved by 2030.

10.8 Mucosal vaccine adjuvants

Presence of double edged sword with poor immunogenicity and evasion phenomenon produced by the worms. Large number of immunomodulatory supplemental molecules, known as Adjuvants, are tried to enhance antigenic processing, recognition, antigen presentation (APC) and immune cell activation through the PAMPs and DAMPs presence. These supplemental material scan be divided into two classes: (i) adjuvants that facilitates vaccine delivery through Liposomes, nanogels, oil-in-water emulsions and (ii) virosomes that stimulates the immune system that includes molecules binding to intracellular receptors including Toll-like receptors (TLRs), Nod-like receptors, and RIG-I–like receptors and to cytosolic DNA sensors [170].

10.9 Microbiome/microbial role

The proteins of the human microbiome, especially the gastrointestinal microbiome, the human proteome, and the immunoglobulin repertoire are also continually processed by APCs and presented to T cells [62, 63]. In examining the immunoglobulinome, it emerged that there is a frequency hierarchy of TCEM. This includes, at one extreme, common motifs found in most immunoglobulin variable regions. These are not limited to motifs encoded by the germline but also include motifs produced by somatic mutation. At the other extreme, very rare motifs are encountered only once in several million B-cell clones [171].

11. Conclusion

The various kinds of parasitic diseases (GIT or hemo-parasites) mean continuous threat for goats and goat keepers in all over the world for goat Industry. The helminthiasis in caprine is one the prime problem for goat breeders and sheep breeders in the goat and sheep rearing community and countries. These parasites not only pose a problem to goat(s) but a continuous threat for serious damage to their lives causing weakened immune response, less resistance and a great chance for various kinds of parasites not only to harbor in the body of host (goat) but also find a safe place to multiply and reproduce. In parallel to these immune responses in body there is ever increasing demand of using and developing various anthelmintics and vermifuges to curb the ever increasing list of parasites. So the animal immunity or production of resistance either in form of breeds development or discovery of innovative broad spectrum medication or production of vaccines has always been in focus since old and have got a big importance. The immunity in body of host (goat and sheep) plays a very decisive role regarding the selection process against the specific parasites prevalent in the area or on the animal health and on the use of medication. There are or could be several factors in the background of immunity in the body of goat which has been demonstrated by various figures present in the test to understand the mechanism(s) happening in the body in real time. We as authors tried best to demonstrate the up dated knowledge in the chapter for the better understanding of viewers or scientists working or intending to work on very sensitive issue of immunity in the body of animal or goat.

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References

[1] Tekola B. On the Importance of Small Ruminant Production and PPR Control and Eradication. New York: Food and Agriculture Organization, UNO; 2015. Available from: https://www.oie.int/eng/PPR2015/Presentation/1.1_Presentation_B-Tekola.pdf; https://www.fao.org

[2] Http://Foa.Org. Distribution of Helminths and Impact of Helminth Diseases on Livestock in Developing Countries

[3] Rankins DL Jr, Pugh DG. Feeding and nutrition. In: Sheep and Goat Medicine. St. Louis MO, USA: WB Saunders; 2012. pp. 18-49

[4] Hoste H, Sotiraki S, Landau SY, Jackson F, Beveridge I. Goat–nematode interactions: Think differently. Trends in Parasitology. 2010;**26**:376-381. DOI: 10.1016/j.pt.2010.04.007

[5] Hadjigeorgion I, Fortatos E, Chatzigeorgiou T. Renovating grazing lands on the Greek islands through the introduction of forage legumes, conference presented Grassland resources for extensive farming systems in marginal lands: Major drivers and future scenarios. In: Proceedings of the 19th Symposium of the European Grassland Federation, 7-10 May; Alghero, Italy. 2017

[6] Smith MC, Sherman DM. Blood, lymph, immune systems. In: Goat Medicine. Hoboken, NJ, USA: Blackwell Publishing was acquired by John Wiley & Sons; 2009. p. 275 (Chapter 7)

[7] Ribeiro MN, Ribeirob NL, Bozzi R, Costa RG. Physiological and biochemical blood variables of goats subjected to heat stress—A review. Journal of Applied Animal Research. 2018;**46**:1036-1041. DOI: 10.1080/09712119.2018.1456439

[8] Zoidis E, Hadjigeorgiou I. Effects of drinking saline water on food and water intake, blood and urine electrolytes and biochemical and haematological parameters in goats: A preliminary study. Animal Production Science [Internet]. CSIRO Publishing; 2018;**58**(10):1822. Available from: http://dx.doi.org/10.1071/an16539

[9] Jain A, Pasare C. Innate control of adaptive immunity: Beyond the three-signal paradigm. Journal of Immunology. 2017;**198**:3791-3800. DOI: 10.4049/jimmunol.1602000

[10] Etim NAN, Williams ME, Akpabio U, Offiong EEA. Haematological parameters and factors affecting their values. Agricultural Science. 2014;**2**:37-47

[11] Hoste H, Torres-Acosta JFJ, Aguilar-Caballero AJ. Nutrition–parasite interactions in goats: Is immunoregulation involved in the control of gastrointestinal nematodes? Parasite Immunology. 2008;**30**:79-88. DOI: 10.1111/j.1365-3024.2007.00987.x

[12] Grencis RK. Immunity to helminths: Resistance, regulation, and susceptibility to gastrointestinal nematodes. Annual Review of Immunology. 2015;**33**:201-225

[13] Hernández-Castellano LE, Moreno-Indias I, Sánchez-Macías D, Morales-delaNuez A, Torres A, Argüello A, et al. Sheep and goats raised in mixed flocks have diverse immune status around parturition. Journal of Dairy Science [Internet]. American Dairy Science Association; Sep 2019;**102**(9): 8478-8485. Available from: http://dx.doi.org/10.3168/jds.2019-16731

[14] Maizels RM, Smits HH, McSorley HJ. Modulation of host immunity by helminthes: The expanding repertoire of parasite effector molecules. Immunity. 2018;**49**:801-819. DOI: 10.1016/j.immuni.2018.10.016

[15] Maizels RM, McSorley HJ. Regulation of the host immune system by helminth parasites. The Journal of Allergy and Clinical Immunology. 2016;**138**:666-675. DOI: 10.1016/j.jaci.2016.07.007

[16] Eke SS, Omalu ICJ, Ochaguba JE, Urama AC, Hassan SC, Otuu CA, et al. Prevalence of gastrointestinal parasites of sheep and goats slaughtered in Minna Modern Abattoir, Niger State, Nigeria. Journal of Animal Science and Veterinary Medicine. 2019;**4**(2):65-70. DOI: 10.31248/JASVM2019.131

[17] Rapin A, Harris NL. Helminth–bacterial interactions: Cause and consequence. Trends Immunology. 2018;**39**:724. DOI: 10.1016/j.it.2018.06.002

[18] Fthenakis GC, Papadopoulos E. Impact of parasitism in goat production. Small Ruminant Research [Internet]. Elsevier BV; Jun 2018;**163**:21-23. Available from: http://dx.doi.org/10.1016/j.smallrumres.2017.04.001

[19] Bishop SC, Morris CA. Genetics of disease resistance in sheep and goats. Small Ruminant Research. 2007;**70**:48-59. DOI: 10.1016/j.smallrumres.2007.01.006

[20] Atanásio-Nhacumbe A, Sitoe CF. Prevalence and seasonal variations of eggs of gastrointestinal nematode parasites of goats from smallholder farms in Mozambique. Insight-Veterinary Science. 2019;**3**:023-029. DOI: 10.29328/journal.ivs.1001016

[21] Sohail M, Nauman-ul-Islam M, Shah SSA, Shah IA, Raziq A, Ilyas M. Incidence of gastrointestinal parasites in beetal goats at district Peshawar, Pakistan. Advances in Animal and Veterinary Sciences. 2017;**5**(5):205-207. DOI: 10.17582/journal.aavs/2017/5.5.205.207

[22] Smith MC, Sherman DM. Goat Medicine. 2nd ed. Hoboken, NJ, USA: Wiley Blackwell; 2019. ISBN-13: 978-0781796439, ISBN-10: 9780781796439

[23] Muriuki C, Bush SJ, Salavati M, McCulloch MEB, Lisowski ZM, Agaba M, et al. A mini-atlas of gene expression for the domestic goat (*Capra hircus*) reveals transcriptional differences in immune signatures between sheep and goats. Cold Spring Harbor Laboratory; 25 Jul 2019; Available from: http://dx.doi.org/10.1101/711127

[24] Patterson DM, Jackson F, Huntley JF, Stevenson LM, Jones DG, Jackson E, et al. The response of breeding does to nematodiasis: Segregation into "Responders" and "non-responders". International Journal for Parasitology. 1996;**26**(11):1295-1303. DOI: 10.1016/s0020-7519(96)00125-7

[25] TN MN, Nisbet AJ. Immune modulation by helminth parasites of ruminants: implications for vaccine development and host immune competence. Parasite. 2014;**21**:51. DOI: 10.1051/parasite/2014051

[26] Marcilla A, Trelis M, Cortés A, Sotillo J, Cantalapiedra F, et al. Extracellular vesicles from parasitic Helminths contain specific excretory/secretory proteins and are internalized in intestinal host cells. PLoS One. 2012;**7**(9):e45974. DOI: 10.1371/journal.pone.0045974

[27] Halim TYF, Hwang YY, Scanlon ST, Zaghouani H, Garbi N, Fallon PG, et al. Group 2 innate lymphoid cells license dendritic cells to potentiate memory T helper 2 cell responses. Nature Immunology. 2016;**17**(1):57-64. DOI: 10.1038/ni.3294

[28] Mishra PK, Palma M, Bleich D, Loke P, Gause WC. Systemic impact of intestinal helminth infections. Mucosal Immunology. 2014;**7**:753. DOI: 10.1038/mi.2014.2

[29] Campbell L, Hepworth MR, Whittingham-Dowd J, Thompson S, Bancroft AJ, Hayes KS, et al. ILC2s mediate systemic innate protection by priming mucus production at distal mucosal sites. Journal of Experimental Medicine [Internet]. Rockefeller University Press; 3 Oct 2019;**216**(12):2714-2723. Available from: http://dx.doi.org/10.1084/jem.20180610

[30] McDonald DR, Levy O. Innate immunity. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, editors. Clinical Immunology—Principles and Practice. 5th ed. Amsterdam, Netherlands: Elsevier Publishing, USA Book Rich; 2019 (Chapter 3)

[31] Herbert DR, Douglas B, Zullo K. Group 2 innate lymphoid cells (ILC2): Type 2 immunity and Helminth immunity. International Journal of Molecular Sciences. 2019;**20**:2276. DOI: 10.3390/ijms20092276

[32] Modena BD, Dazy K, White AA. Emerging concepts: mast cell involvement in allergic diseases. Translational Research. 2016;**174**:98. DOI: 10.1016/j.trsl.2016.02.011

[33] Löser S, Smith KA, Maizels RM. Innate lymphoid cells in Helminth infections—Obligatory or accessory? Frontiers in Immunology [Internet]. Frontiers Media SA; 10 Apr 2019;**10**. Available from: http://dx.doi.org/10.3389/fimmu.2019.00620

[34] Chen D, Tian A-L, Hou J-L, Li J-X, Tian X, Yuan X-D, et al. The multitasking *Fasciola gigantica* cathepsin B interferes with various functions of goat peripheral blood mononuclear cells in vitro. Frontiers in Immunology [Internet]. Frontiers Media SA; 23 Jul 2019;**10**. Available from: http://dx.doi.org/10.3389/fimmu.2019.01707

[35] Choubey S, Beniwal V, Sharma AK. Immunity. In: Sharma AK, editor. Immunology: An Introductory Textbook. Singapore: Pan Stanford Publishing, Taylor and Francis Group; 2019. pp. 19-31 (Chapter 2)

[36] Bernink JH, Germar K, Spits H. The role of ILC2 in pathology of type 2 inflammatory diseases. Current Opinion in Immunology. 2014;**31**:115-120. DOI: 10.1016/j.coi.2014.10.007

[37] Hoyler T, Connor CA, Kiss EA, Diefenbach A. T-bet and Gata3 in controlling type 1 and type 2 immunity mediated by innate lymphoid cells. Current Opinion in Immunology. 2013;**25**(2):139-147. DOI: 10.1016/j.coi.2013.02.007

[38] Robinette ML, Fuchs A, Cortez VS, Lee JS, Wang Y, Durum SK, et al. The immunological genome consortium. Transcriptional programs define molecular characteristics of innate lymphoid cell classes and subsets. Nature Immunology. 2015;**16**(3):306-317. DOI: 10.1038/ni.3094

[39] Gasteiger G, Fan X, Dikiy S, Lee SY, Rudensky AY. Tissue residency of innate lymphoid cells in lymphoid and nonlymphoid organs. Science. 2015;**350**:981-985. DOI: 10.1126/science.aac9593

[40] Bar-Ephraïm YE, Mebius RE. Innate lymphoid cells in secondary lymphoid organs. Immunological Reviews. 2016;**271**(1):185-199. Available from: http://dx.doi.org/10.1111/imr.12407

[41] Huang L, Gebreselassie NG, Gagliardo LF, Ruyechan MC, Luber KL, Lee NA, et al. Eosinophils mediate protective immunity against secondary nematode infection. Journal of Immunology. 2015;**194**:283-290. DOI: 10.4049/jimmunol.1402219

[42] Germain RN, Huang Y. ILC2s—Resident lymphocytes pre-adapted to a specific tissue or migratory effectors that adapt to where they move? Current Opinion in Immunology. 2019;**56**:76-81. DOI: 10.1016/j.coi.2018.11.001

[43] Chou C, Li MO. Re(de)fining innate lymphocyte lineages in the face of cancer. Cancer Immunology Research. 2018;**6**:372. DOI: 10.1158/2326-6066.CIR-17-0440

[44] Nehra AK, Gowane GR, Kuriyal A, Chaurasiya A, Kumar R, Bhinsara DB, et al. Immune response against subclinical haemonchosis in Himalayan hill goats. Veterinary Parasitology [Internet]. Elsevier BV; Mar 2019;**267**:47-53. Available from: http://dx.doi.org/10.1016/j.vetpar.2019.01.005

[45] Homan EJ, Bremel RD. A role for epitope networking in immunomodulation by Helminths. Frontiers in Immunology. 2018;**9**:1763. DOI: 10.3389/fimmu.2018.0176.3

[46] Bozza MT, Lintomen L, Kitoko JZ, Paiva CN, Olsen PC. The role of MIF on eosinophil biology and eosinophilic inflammation. Clinical Reviews in Allergy & Immunology [Internet]. Springer Science and Business Media LLC; 25 Jan 2019;**58**(1):15-24. Available from: http://dx.doi.org/10.1007/s12016-019-08726-z

[47] Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. Nature Reviews. Immunology. 2011;**11**:375-388. DOI: 10.1038/nri2992

[48] McRae KM, Stear MJ, Good B, Keane OM. The host immune response to gastrointestinal nematode infection in sheep. Parasite Immunology. 2015;**37**:605-613

[49] Bar-Ephraim YE, Konijn T, Gönültas M, Mebius RE, Reijmers RM. A reproducible method for isolation and in vitro culture of functional human lymphoid stromal cells from tonsils. Fritz JH, editor. PLOS ONE; 2016;**11**(12):e0167555. DOI: 10.1371/journal.pone.0167555

[50] Pearce EJ. T_H 2 cell responses in immunity and inflammation following Helminth infection. In: Gause WC, Artis D, editors. The T_H 2 Type Immune Response in Health and Disease. New York: Springer Science+Business Media; 2016. p. 53. DOI: 10.1007/978-1-4939-2911-5_4

[51] Filbey KJ, Grainger JR, Smith KA, Boon L, Rooijen N, Harcus Y, et al. Innate and adaptive type 2 immune cell responses in genetically controlled resistance to intestinal helminth infection. Immunology and Cell Biology. 2014;**92**:436-448. DOI: 10.1038/icb.2013.109

[52] Hepworth MR, Daniłowicz-Luebert E, Rausch S, Metz M, Klotz C, Maurer M, et al. Mast cells orchestrate type 2 immunity to helminths through regulation of tissue-derived cytokines. PNAS. 2012;**109**:6644-6649. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1112268109

[53] Zaiss MM, Maslowski KM, Mosconi I, Guenat N, Marsland BJ, et al. IL-1β suppresses innate IL-25 and IL-33 production and maintains Helminth chronicity. PLoS Pathogens. 2013;**9**(8):e1003531. DOI: 10.1371/journal.ppat.1003531

[54] Kabata H, Moro K, Koyasu S. The group 2 innate lymphoid cell (ILC2) regulatory network and its underlying mechanisms. Immunological Reviews. 2018;**286**:37-52. DOI: 10.1111/imr.12706

[55] Swiecki M, Colonna M. The multifaceted biology of plasmacytoid dendritic cells. Nature Reviews. Immunology. 2015;**15**(8):471-485. DOI: 10.1038/nri3865

[56] Nagasawa M, Spits H, Ros XR. Innate lymphoid cells (ILCs): Cytokine hubs regulating immunity and tissue homeostasis. innate lymphoid cells (ILCs): Cytokine hubs regulating immunity and tissue homeostasis. Cold Spring Harbor Perspectives in Biology. 2017:a030304 [Internet]. Cold Spring Harbor Laboratory; 11 Dec

2017;**10**(12):a030304. Available from: http://dx.doi.org/10.1101/cshperspect.a030304

[57] Bar-On L, Birnberg T, Lewis KL, Edelson BT, Bruder D, Hildner K, et al. CX_3CR1^+ $CD8\alpha^+$ dendritic cells are a steady-state population related to plasmacytoid dendritic cells. Proceedings of the National Academy of Sciences [Internet]. 2 Aug 2010;**107**(33):14745-14750. Available from: http://dx.doi.org/10.1073/pnas.1001562107

[58] Wang W, Yuan C, Wang S, Song X-K, Xu L-X, Yan R-F, et al. Transcriptional and proteomic analysis reveal recombinant galectins of Haemonchus contortus down-regulated functions of goat PBMC and modulation of several signaling cascades *in vitro*. Journal of Proteomics. 2014;**98**:123-137. DOI: 10.1016/j.jprot.2013.12.017

[59] Summerfield A, Auray G, Ricklin M. Comparative dendritic cell biology of veterinary mammals. Annual Review of Animal Biosciences. 2015;**3**:7.1-7.25. DOI: 10.1146/annurev-animal-022114-111009

[60] Motran CC, Silvane L, Chiapello LS, Theumer MG, Ambrosio LF, Volpini X, et al. Helminth infections: Recognition and modulation of the immune response by innate immune cells. Frontiers in Immunology. 2018;**9**:664. DOI: 10.3389/fimmu.2018.00664

[61] Koyasu S, Moro K. Type 2 innate immune responses and the natural helper cell. Immunology;**132**:475-481. DOI: 10.1111/j.1365-2567.2011.03413.x

[62] Dietz CP, Luong A. Innate lymphoid cells: The innate counterpart to T helper cells. Advances in Oto-Rhino-Laryngology. 2016;**79**:58-68. DOI: 10.1159/000445130

[63] Ayaz MM, Nazir MM, Samad N, Zubair M, Hanif M, Aziz M, et al. Parasitism in goats and its effect by management and control. In: Kukovics S, editor. Goat Science. London, UK: InTech Biosciences; 2018 (Chapter 13)

[64] Olsen L. Investigation of the gut-associated lymphoid tissue in sheep with emphasis on natural killer cells [PhD thesis]. Norway: Department of Basic Sciences and Aquatic Medicine Faculty of Veterinary Medicine and Biosciences Norwegian University of Life Sciences; 2015

[65] Kim CH, Hashimoto-Hill S, Kim M. Migration and tissue tropism of innate lymphoid cells. Trends in Immunology. 2016;**37**(1):68-79. DOI: 10.1016/j.it.2015.11.003

[66] Cerovic V, Mowat AM, Milling SWF. Intestinal macrophages and dendritic cells: what's the difference? Trends in Immunology. 2014;**35**(6):270-277. DOI:10.1016/j.it.2014.04.003

[67] Kabat AM, Pott J, Maloy KJ. The mucosal immune system and its regulation by autophagy. Frontiers in Immunology. 2016;**7**:240. DOI: 10.3389/fimmu.2016.00240

[68] Park EJ, Kawamoto E, Shimaoka M. Mucosal immunity for inflammation: regulation of gut-specific lymphocyte migration by integrins. In: Mucosal Vaccines (Second Edition), Innovation for Preventing Infectious Diseases. Cambridge, MA, USA: Academic Press; 2020. pp. 85-99. DOI: 10.1016/B978-0-12-811924-2.00005-5 (Chapter 5)

[69] Smith KA, Harcus Y, Garbi N, Hämmerling GJ, MacDonald AS, Maizels RM. Type 2 innate immunity in Helminth infection is induced redundantly and acts autonomously following $CD11c^+$ cell depletion. Infection and Immunity. 2012;**80**:3481-3489. DOI: 10.1128/IAI.00436-12

[70] Dezfuli BS, Bo T, Lorenzoni M, Shinn AP, Giari L. Fine structure and cellular responses at the host–parasite interface in a range of fish–helminth systems. Veterinary Parasitology. 2015;**208**:272-279. DOI: 10.1016/j.vetpar.2015.01.002

[71] Masopust D, Soerens AG. Tissue-resident T cells and other resident leukocytes. Annual Review of Immunology. 2019;**37**:521-546. DOI: 10.1146/annurev-immunol-042617053214

[72] Redpathh SA, Heieis GA, Reynolds LA, Fonseca NM, Kim SS-Y, Perona-Wright G. Functional specialization of intestinal dendritic cell subsets during Th2 helminth infection in mice. European Journal of Immunology. 2018;**48**:87-98. DOI: 10.1002/eji.201747073

[73] Ko H-J, Chang S-Y. Regulation of intestinal immune system by dendritic cells. Immune Network. 2015;**15**:1-8. DOI: 10.4110/in.2015.15.1.1

[74] Zakeri A, Hansen EP, Andersen SD, Williams AR, Nejsum P. Immunomodulation by helminthes: Intracellular pathways and extracellular vesicles. Frontiers in Immunology. 2018;**9**:2349. DOI: 10.3389/fimmu.2018.02349

[75] Zakeri A, Yazdi FG. Toll-like receptor-mediated involvement of innate immune cells in asthma disease. Biochimica et Biophysica Acta (BBA)-General Subjects. 2017;**1861**:3270-3277

[76] Oliveira SC, Figueiredo BC, Cardoso LS, Carvalho EM. A double edged sword: *Schistosoma mansoni* Sm29 regulates both Th1 and Th2 responses in inflammatory mucosal diseases. Mucosal Immunology;**9**(6):1366-1371. DOI: 10.1038/mi.2016.69

[77] Coakley G, Maizels RM, Buck AM. Exosomes and other extracellular vesicles: The new communicators in parasite infections, Trends in Parasitology. 2015;**31**:477. DOI: 10.1016/j.pt.2015.06.009 477

[78] Mekonnen GG, Pearson M, Loukas A, Sotillo J. Extracellular vesicles from parasitic helminths and their potential utility as vaccines. Expert Review of Vaccines. 2018;**17**:197-205. DOI: 10.1080/14760584.2018.1431125

[79] Silva VO, Maia MM, Torrecilhas AC, Taniwaki NN, Namiyama GM, Oliveira KC, et al. Extracellular vesicles isolated from *Toxoplasma gondii* induce host immune response. Parasite Immunology. 2018;**40**:e12571. DOI: 10.1111/pim.12571

[80] Gazzinelli-Guimaraes PH, Nutman TB. Helminth parasites and immune regulation [version 1; referees: 2 approved]. F1000 Research. 2018;7(F1000 Faculty Rev):1685. DOI: 10.12688/f1000research.15596.1

[81] Coakley G, McCaskill JL, Borger JG, Simbari F, Robertson E, Millar M, et al. Cell Reports. 2017;**19**:1545-1557. DOI: 10.1016/j.celrep.2017.05.001

[82] Kifle DW, Sotillo J, Pearson MS, Loukas A. Extracellular vesicles as a target for the development of anti-helminth. Emerging Topics in Life Sciences. 2017;**1**:659-665. DOI: 10.1042/ETLS20170095

[83] Eichenberger RM, Ryan S, Jones L, Buitrago G, Polster R, Montes de Oca M, et al. Hookworm secreted extracellular vesicles interact with host cells and prevent inducible colitis in mice. Frontiers in Immunology. 2018;**9**:850. DOI: 10.3389/fimmu.2018.00850

[84] Buck ED, Anné J, Lammertyn E. The role of protein secretion systems in the virulence of the intracellular pathogen *Legionella pneumophila*. Microbiology. 2007;**153**:3948-3953. DOI: 10.1099/mic.0.2007/012039-0

[85] Ramesh M. Mechanisms of parasite immune-modulation and evasion [PhD thesis]. Fort Worth, Texas, USA: Texas Christian University; 2018

[86] Meeusen ENT, Walker J, Peters A, Pastoret P-P, Jungersen J. Current status of veterinary vaccines. Clinical Microbiology Reviews. 2007;**20**:489-510. DOI: 10.1128/CMR.00005-07

[87] Schmidt C. Immunoproteasome function in lymphocyte activation [PhD thesis]. University of Konstanz, Germany: Mathematisch-Naturwissenschaftliche Sektion, Fachbereich Biologie; 2018. Available from: http://nbn-resolving.de/urn:nbn:de:bsz:352-2-3cw92n75tqfq9

[88] Scheerlinck J-PY. The immune system of sheep and goats. Encyclopedia of Immunobiology [Internet]. Elsevier; 2016:526-531. Available from: http://dx.doi.org/10.1016/b978-0-12-374279-7.12017-x

[89] Thornton DJ, Rousseau K, McGuckin MA. Structure and function of the polymeric mucins in airways mucus. Annual Review of Physiology. 2008;**70**:459-486. DOI: 10.1146/annurev.physiol.70.113006.100702

[90] Sharpe C, Thornton DJ, Grencis RK. A sticky end for gastrointestinal helminthes; the role of the mucus barrier. Parasite Immunology. 2018;**40**:e12517. DOI: 10.1111/pim.12517

[91] Brosschot TP, Reynolds LA. The impact of a helminth-modified microbiome on host immunity. Mucosal Immunology. 2018;**11**:1039-1046. DOI: 10.1038/s41385-018-0008-5

[92] Atuma C, Strugala V, Allen A, Holm L. The adherent gastrointestinal mucus gel layer: Thickness and physical state in vivo. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2001;**280**:G922-G929

[93] Patra G, Alam SS, Borthakur SK, Prasad H. Studies on antigenic cross-reactivity of *Trichuris ovis* with host mucosal antigens in goat. Asian Pacific Journal of Tropical Disease. 2015;**5**:935-939. DOI: 10.1016/s2222-1808(15)60961-6

[94] Theodoropoulos G, Hicks SJ, Corfield AP, Miller BG, Carrington SD. The role of mucins in host–parasite interactions: Part II—Helminth parasites. Trends in Parasitology. 2001;**17**(3):130-135. DOI: 10.1016/s1471-4922(00)01775-x

[95] Harrington EP, Bergles DE, Calabresi PA. Immune cell modulation of oligodendrocyte lineage cells. Neuroscience Letters [Internet]. Elsevier BV; Jan 2020;**715**:134601. Available from: http://dx.doi.org/10.1016/j.neulet.2019.134601

[96] Babu S, Nutman TB. Immune responses to helminth infection. In: Rich RR, Fleisher TA, Shearer WT, Schroeder HW, Frew AJ, Weyand CM, editors. Clinical Immunology. 5th ed. China: Elsevier Ltd; 2019. pp. 437-447 (Chapter 31)

[97] Leventhal DS, Gilmore DC, Berger JM, Nishi S, Lee V, Malchow S, et al. Dendritic cells coordinate the development and homeostasis of organ-specific regulatory T cells. Immunity [Internet]. Elsevier BV; Apr 2016;**44**(4):847-859. Available from: http://dx.doi.org/10.1016/j.immuni.2016.01.025

[98] Rũckerl D, Campbell SM, Duncan S, Sutherland TE, Jenkins SJ, Hewitson JP, et al. Macrophage origin limits functional plasticity in helminth-bacterial co-infection. PLoS Pathogens. 2017;**13**(3):e1006233. DOI: 10.1371/journal. ppat.1006233

[99] Ryszer T. Understanding the mysterious M2 macrophage through activation markers and

effector mechanisms. Mediators of Inflammation. 2015;Article ID 816460. DOI: 10.1155/2015/816460

[100] Oyesola OO, Früh SP, Webb LM, Tait Wojno ED. Cytokines and beyond: Regulation of innate immune responses during helminth infection. Cytokine [Internet]. Elsevier BV; Sep 2018. Available from: http://dx.doi.org/10.1016/j.cyto.2018.08.021

[101] Grencis RK, Humphreys NE, Bancroft AJ. Immunity to gastrointestinal nematodes: Mechanisms and myths. Immunological Reviews. 2014;**260**:183-205

[102] Zakeri A, Hansen EP, Andersen SD, Williams AR, Nejsum P. Immunomodulation by Helminths: Intracellular pathways and extracellular vesicles. Frontiers in Immunology. 2018;**9**:2349. DOI: 10.3389/fimmu.2018.02349

[103] Cortés A, Muñoz-Antoli C, Esteban JG, Toledo R. T_H 2 and T_H 1 responses: Clear and hidden sides of immunity against intestinal Helminths. Trends in Parasitology [Internet]. Elsevier BV; Sep 2017;**33**(9):678-93. Available from: http://dx.doi.org/10.1016/j.pt.2017.05.004

[104] Allen JE, Maizels RM. Diversity and dialogue in immunity to helminthes. Nature Reviews Immunology. 2011;**11**:375

[105] Jackson JA, Fribergn IM, Little S, Bradley JE. Review series on helminths, immune modulation and the hygiene hypothesis: Immunity against helminths and immunological phenomena in modern human populations: Coevolutionary legacies? Immunology. 2008;**126**:18-27. DOI: 10.1111/j.1365-2567.2008.03010.x

[106] Pelly VS, Coomes SM, Kannan Y, Gialitakis M, Entwistle LJ, Perez-Lloret J, et al. Interleukin 4 promotes the development of ex-Foxp3 Th2 cells during immunity to intestinal helminths. The Journal of Experimental Medicine [Internet]. Rockefeller University Press; 15 May 2017;**214**(6):1809-1826. Available from: http://dx.doi.org/10.1084/jem.20161104

[107] Klose CSN, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. Nature Immunology. 2016;**17**:765-774. DOI: 10.1038/ni.3489

[108] Ramanan D, Bowcutt R, Lee SC, Tang MS, Kurtz ZD, Ding Y, et al. Helminth infection promotes colonization resistance via Type 2 immunity. Science. 2016;**352**:608-612. DOI: 10.1126/science.aaf3229

[109] McGuckin M, Lindén S, Sutton P, et al. Mucin dynamics and enteric pathogens. Nature Reviews. Microbiology. 2011;**9**:265-278. DOI: 10.1038/nrmicro2538

[110] McSorley HJ, Chayé MAM, Smits HH. Worms: Pernicious parasites or allies against allergies? Parasite Immunology. 2019;**41**:e12574. DOI: 10.1111/pim.12574

[111] Geremia A, ArancibiaCárcamo CV. Innate lymphoid cells in intestinal inflammation. Frontiers in Immunology. 2017;**8**:1296. DOI: 10.3389/fimmu.2017.01296

[112] Mitruka BM, Rawnsley HM. Clinical Biochemical and Hematological Values in Normal Experimental Animals and Normal Humans. New York: Madison Publishing USA; 1981

[113] Onasanya GO, Oke FO, Sanni TM, Muhammad AI. Parameters influencing haematological, serum and biochemical references in livestock animals under different management systems. Open Journal of Veterinary Medicine. 2015;**5**:181-189. DOI: 10.4236/ojvm.2015.58025

[114] Iliev PT, Georgieva TM. Acute phase proteins in sheep and goats—Function, reference ranges and assessment methods: An overview. Bulgarian Journal of Veterinary Medicine. 2018;**21**(1):1-16. DOI: 10.15547/bjvm.1050

[115] Schwartz JC, Philp RL, Bickhart DM, Smith TPL, Hammond JA. The antibody loci of the domestic goat (*Capra hircus*). Immunogenetics. 2018;**70**:317-326. DOI: 10.1007/s00251-017-1033-3

[116] Micusan GVV, Borduas AG. Biological properties of goat immunoglobulins. Immunology. 1977;**32**:373

[117] He J, Subramaniam S, Narang V, et al. IgG1 memory B cells keep the memory of IgE responses. Nature Communications. 2017;**8**:641. DOI: 10.1038/s41467-017-00723-0

[118] Konishi M, Tsuduku S, Haritani M, Murakami K, Tsuboi T, Kobayashi C, et al. An epidemic of caprine arthritis encephalitis in Japan: Isolation of the virus. The Journal of Veterinary Medical Science. 2004;**66**:911-917

[119] Haley PJ. The lymphoid system: A review of species differences. Journal of Toxicologic Pathology. 2017;**30**:111-123. DOI: 10.1293/tox.2016-00755

[120] Figueiredo JF, Barnhart KF, Tripathi N. Clinical pathology assays in immunopathology. In: Immunopathology in Toxicology and Drug Development. Cham: Humana Press; 2017. pp. 457-488

[121] Artis D, Spits H. The biology of innate lymphoid cells. Nature. 2015;**517**:293-301. DOI: 10.1038/nature141899

[122] Griot-Wenk ME, Obexer-Ruff G, Fluri A, Marti E. Partial sequences of feline and caprine immunoglobulin epsilon heavy chain cDNA and comparative binding studies of recombinant IgE fragment-specific antibodies across different species. Veterinary Immunology and Immunopathology [Internet]. Elsevier BV; Jun 2000;**75**(1-2):59-69. Available from: http://dx.doi.org/10.1016/s0165-2427(00)00183-5

[123] Hernández-Castellano LE, Moreno-Indias I, Sánchez-Macías D, Morales-delaNuez A, Torres A, Argüello A, et al. Sheep and goats raised in mixed flocks have diverse immune status around parturition. Journal of Dairy Science [Internet]. American Dairy Science Association; Sep 2019;**102**(9):8478-8485. Available from: http://dx.doi.org/10.3168/jds.2019-16731

[124] Baliu-Piquéa M, Kurniawana H, Ravesloot L, Verheij MW, Drylewicz J, Lievaart-Peterson K, et al. Age-related distribution and dynamics of T-cells in blood and lymphoid tissues of goats. Developmental and Comparative Immunology. 2019;**93**:1-10. DOI: 10.1016/j.dci.2018.12.004

[125] Gagnon JD, Ansel KM. MicroRNA regulation of CD8+ T cell responses. Non-coding RNA Investigation. 2019;**3**:24. DOI: 10.21037/ncri.2019.07.02

[126] Griffiths-Jones S, Saini HK, Dongen S, Enright AJ. miRBase: Tools for microRNA genomics. Nucleic Acids Research. 2008;**36**:D154-D158. DOI: 10.1093/nar/gkm952

[127] Wara AB, Chhotaray S, Shafi SD, Panda S, Tarang M, Yosuf S, et al. Role of miRNA signatures in health and productivity of livestock. International Journal of Current Microbiology and Applied Sciences. 2019;**8**:727-738. DOI: 10.20546/ijcmas.2019.804.079

[128] Liu Q, Tuo W, Gao H, Zhu X-Q. MicroRNAs of parasites: Current status and future perspectives. Parasitology Research. 2010;**107**:501-507. DOI: 10.1007/s00436-010-1927-6

[129] Contreras J, Rao DS. MicroRNAs in inflammation and immune responses. Leukemia. 2011;**26**(3):404-413. DOI: 10.1038/leu.2011.356

[130] Lu L-F, Liston A. MicroRNA in the immune system, microRNA as an immune system. Immunology. 2009;**127**:291-298. DOI: 10.1111/j.1365-2567.2009.03092.x

[131] Belver L, Papavasiliou FN, Ramiro AR. MicroRNA control of lymphocyte differentiation and function. Current Opinion in Immunology. 2011;**23**(3):368-373. DOI: 10.1016/j.coi.2011.02.001

[132] Self-Fordham JB, Naqvi AR, Uttamani JR, Kulkarni V, Nares S. MicroRNA: Dynamic regulators of macrophage polarization and plasticity. Frontiers in Immunology. 2017;**8**:1062. DOI: 10.3389/fimmu.2017.01062

[133] Arora N, Tripathi S, Singh AK, Mondal P, Mishra A, Prasad A. Micromanagement of immune system: Role of miRNAs in helminthic infections. Frontiers in Microbiology. 2017;**8**:586. DOI: 10.3389/fmicb.2017.00586

[134] Naina A, Shweta T, Singh Aloukick K, Prosenjit M, Amit M, Amit P. Micromanagement of immune system: Role of miRNAs in helminthic infections. Frontiers in Microbiology. 2017;**8**:586

[135] Pak JH, Kim IK, Kim SM, Maeng S, Song KJ, Na B-K, et al. Induction of cancer-related microRNA expression profiling using excretory-secretory products of *Clonorchis sinensis*. Parasitology Research. 2014;**113**:4447-4455. DOI: 10.1007/s00436-014-4127-y

[136] Cai P, Gobert GN, McManus DP. MicroRNAs in parasitic Helminthiases: Current status and future perspectives. Trends in Parasitology. 2016;**32**(1):71-86. DOI: 10.1016/j.pt.2015.09.003

[137] Hill DG. Investigating mechanisms that regulate ectopic lymphoid-like structures in inflammation [PhD thesis]. UK: Cardiff University; 2019

[138] Xu MJ, Liu Q, Nisbet AJ, Cai XQ, Yan C, Lin RQ, et al. Identification and characterization of microRNAs in *Clonorchis sinensis* of human health significance. BMC Genomics. 2010;**11**:521. DOI: 10.1186/1471-2164-11-521

[139] Zheng Y, Cai X, Bradley JE. microRNAs in parasites and parasite infection. RNA Biology. 2013;**10**(3):371-379. DOI: 10.4161/rna.23716

[140] Kirigin FF, Lindstedt K, Sellars M, Ciofani M, Low SL, Jones L, et al. Dynamic microRNA gene transcription and processing during T cell development. Journal of Immunology. 2012;**188**:3257-3267. DOI: 10.4049/jimmunol.1103175

[141] Podshivalova K, Salomon DR. microRNA regulation of T lymphocyte immunity: modulation of molecular networks responsible for T cell activation, differentiation and development. Critical Reviews in Immunology. 2013;**33**(5):435-476

[142] Inácio DP, Amado T, Silva-Santos B, Gomes AQ. Control of T cell effector functions by miRNAs. Cancer Letters [Internet]. Elsevier BV; Jul 2018;**427**:63-73. Available from: http://dx.doi.org/10.1016/j.canlet.2018.04.011

[143] Baumjohann D, Ansel KM. MicroRNA regulation of T helper cell differentiation and plasticity. Nature Reviews. Immunology. 2013;**13**(9):666-678. DOI: 10.1038/nri3494

[144] Bassoy EY, Towne JE, Gabay C. Regulation and function of interleukin-36 cytokines. Immunological Reviews. 2017;**281**(1):169-178. DOI: 10.1111/imr.12610

[145] Stittrich A-B, Haftmann C, Sgouroudis E, Kühl AA, Hegazy AN, Panse I, et al. The microRNA miR-182 is induced by IL-2 and promotes clonal expansion of activated helper T lymphocytes. Nature Immunology. 2010;**11**:1057-1062. DOI: 10.1038/ni.1945

[146] Mattes J, Collison A, Plank M, Phipps S, Foster PS. Antagonism of microRNA-126 suppresses the effector function of T_H2 cells and the development of allergic airways disease. PNAS. 2009;**106**:18704-18709. DOI: 10.1073.pnas.0905063106

[147] Song W, Craft J. T follicular helper cell heterogeneity: Time, space, and function. Immunological Reviews. 2019;**288**(1):85-96. DOI: 10.1111/imr.12740

[148] Mahesh G, Biswas R. MicroRNA-155: A master regulator of inflammation. Journal of Interferon & Cytokine Research [Internet]. Mary Ann Liebert Inc; Jun 2019;**39**(6):321-330. Available from: http://dx.doi.org/10.1089/jir.2018.0155

[149] Johansson T. Gastrointestinal nematodes in goats in small holder flocks around Gaborone, Botswana [thesis]. Uppsala, Sweden: Faculty of Veterinary Medicine and Animal Science, Depart Biomedical Sci Vet Public Health Swedish University of Agricultural Sciences; 2017. Available from: http://stud.epsilon.slu.se

[150] Li RW, Li W, Sun J, Yu P, Baldwin R, Urban JF. The effect of helminth infection on the microbial composition and structure of the caprine abomasal microbiome. Scientific Reports [Internet]. Springer Science and Business Media LLC; Feb 2016;**6**(1). Available from: http://dx.doi.org/10.1038/srep20606

[151] Rakebrandt N, Joller N. Infection history determines susceptibility to unrelated diseases. BioEssays. 2019;**41**:1800191. DOI: 10.1002/bies.201800191

[152] Hein WR, Harrison GBL. Vaccines against veterinary helminthes. Veterinary Parasitology. 2005;**132**:217-222. DOI: 10.1016/j.vetpar.2005.07.006

[153] Piedrafita D, Spithill TW, Smith RE, Raadsma HW. Improving animal and human health through understanding liver fluke immunology. Parasite Immunology. 2010;**32**:572-581. DOI: 10.1111/j.1365-3024.2010.01223.x

[154] Nieuwhof GJ, Bishop SC. Costs of the major endemic diseases of sheep in Great Britain and the potential benefits of reduction in disease impact. Animal Science. 2005;**81**:23-29. DOI: 10.1079/ASC41010023

[155] Sylvester HJ, Griffith EH, Jacob ME, Foster DM. Factors associated with strongyle infection in goats at the individual and farm level. Journal of the American Veterinary Medical Association. 2018;**253**(7):907-917. DOI: 10.2460/javma.253.7.907

[156] Britton C, Winter AD, Marks ND, Gu H, McNeilly TN, Gillan V, et al. Application of small RNA technology for improved control of parasitic helminthes. Veterinary Parasitology. 2015;**212**:47-45. DOI: 10.1016//j.vetpar.2015.06.003

[157] Pulendran B. Systems biological approaches for mucosal vaccine development. In: Kiyono H, Pascual DW, editors. Mucosal Vaccines, Innovation for Preventing Infectious Diseases. 2nd ed. 2020. pp. 753-772. DOI: 10.1016/B978-0-12-811924-2.00045-6 (Chapter 45)

[158] Johnson-Weaver BT, Abraham SN, Staats HF. Innate immunity-based mucosal modulators and adjuvants. Mucosal Vaccines [Internet]. Elsevier; 2020:167-183. Available

from: http://dx.doi.org/10.1016/b978-0-12-811924-2.00010-9

[159] Sharma N, Singh V, Shyma KP. Role of parasitic vaccines in integrated control of parasitic diseases in livestock. Veterinary World. 2015;**8**(5):590-598. DOI: 10.14202/vetworld.2015.590-598

[160] Singh E, Chandra D, Prasad A, Kaur N. Potential vaccine candidates against nematodes of veterinary importance: An overview. International Journal of Current Microbiology and Applied Sciences. 2019;**8**(4):222-228. DOI: 10.20546/ijcmas.2019.804.023

[161] Dhar DN, Sharma RL. Immunization with irradiated larvae against *Dictyocaulus filaria* in young lambs. Veterinary Parasitology. 1981;**9**:125-131. DOI: 10.1016/0304-4017(81)90031-5

[162] Loukas A, Giacomin P. Developments in the design of anti-helminth vaccines. The Th2 Type Immune Response in Health and Disease [Internet]. New York: Springer; 2016: 97-114. Available from: http://dx.doi.org/10.1007/978-1-4939-2911-5_6

[163] Aboshady HM, Mandonnet N, Stear MJ, Arquet R, Bederina M, Sarry J. Transcriptome variation in response to gastrointestinal nematode infection in goats. PLoS One. 2019;**14**(6):e0218719. DOI: 10.1371/journal.pone.0218719

[164] Shi W, Xue C, Su X-Z, Lu F. The roles of galectins in parasitic infections. Acta Tropica. 2018;**177**:97-104. DOI: 10.1016/j.actatropica.2017.09.027

[165] Die I, Cummings RD. Glycomics in unraveling glycan-driven immune responses by parasitic helminths. In: Cummings RD, Mic J, editors. Handbook of Glycomics. Cambridge, MA, USA: Academic Press; 2010. pp. 367-396. DOI: 10.1016/B978-0-12-373600-0.00015-9 (Chapter 15)

[166] Tritten L, Geary TG. Helminth extracellular vesicles in host–parasite interactions. Current Opinion in Microbiology. 2018;**46**:73-79. DOI: 10.1016/j.mib.2018.08.002

[167] Stutzer C, Richards SA, Ferreira M, Baron S, Maritz-Olivier C. Metazoan parasite vaccines: Present status and future prospects. Frontiers in Cellular and Infection Microbiology. 2018;**8**:67. DOI: 10.3389/fcimb.2018.00067

[168] Vercruysse J, Charlier J, Van Dijk J, Morgan ER, Geary T, von Samson - Himmelstjerna G, et al. Control of helminth ruminant infections by 2030. Parasitology [Internet]. Cambridge University Press (CUP); 8 Feb 2018;**145**(13):1655-1664. Available from: http://dx.doi.org/10.1017/s003118201700227x

[169] Metthews JB, Geldhof P, Tzelos T, Claerebout E. Progress in the development of subunit vaccines for gastrointestinal nematodes of ruminants. Parasite Immunology. 2016;**38**:744-753. DOI: 10.1111/pim.12391

[170] Kim H-J, Baek A, Kim M, Cho S-R. Gene expression profiling for confirmation of effects of DNA polymeric molecules on in vitro arthritis model. Osteoarthritis and Cartilage. 2017;**25**:S417-S419

[171] Homan EJ, Bremel RD. A role for epitope networking in immunomodulation by Helminths. Frontiers in Immunology. 2018;**9**:1763. DOI: 10.3389/fimmu.2018.01763