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Immune response against gastrointestinal nematodes and the potential application of immortalized cell lines in the sheep industry

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Abstract. The world's sheep industry faces significant health challenges due to endoparasite infections. One effective management approach to control these parasites is through the activation of the host's immune system. Vaccination emerges as a potential method to control gastrointestinal nematode (GIN) parasites while addressing the need for animal food products devoid of harmful chemicals. However, the development of an efficient anti-parasite vaccine requires a comprehensive understanding of the immune responses elicited by the sheep to control the GIN infection. Mast cells, recognized as tissue-resident immune cells primarily involved in IgE-mediated immune responses, play a pivotal role in both innate and adaptive immunity. Based on their location and function, mast cells are classified into tissue and mucosal mast cells and play an important role in defending the host against specific pathogens. Mucosal mast cells, located in the body's mucosal surfaces, are capable of initiating early immune responses against bacterial and viral infection, thereby contributing to effective immunity in animals. Advancing our knowledge about mast cell biology through the successful culturing of mast cell lines holds great promise for the sheep industry. It may lead to the development of targeted vaccines that can further improve the productivity, welfare, and economic sustainability of the sheep industry. In this paper, we review the effective immune responses employed by sheep to combat the GIN infections and highlight the crucial roles of mast cells in establishing host immune responses to eliminate the GIN.

Keywords: Mast cells, sheep, gastrointestinal nematode, immortalized cell lines

Classification numbers: 1.1.5, 1.2.5, 3.7.2

1. INTRODUCTION

Sheep are one of the world's primary animal genetic resources and their production plays a pivotal role in meeting global food and fiber demands while contributing to economic

development, sustainable agriculture, and cultural traditions in many regions around the world. Sheep are valued for their wool and fiber and are also a significant source of animal protein, supplying meat and dairy products to diverse populations worldwide [1]. These products contribute to protein enriched diets, particularly in regions where other protein sources may be limited or inaccessible. Sheep are a hardy species that can thrive in marginal lands where they can aid in land management through grazing and contribute to sustainable farming systems by providing food sources in otherwise non-arable land. Their adaptability to diverse climates and ability to utilize poor-quality forage make them resilient and valuable assets to enhance food security and support rural economies, and especially the livelihoods of smallholders in poorer regions [2, 3].

Proteins are a vital component of the human diet which can be sourced from either animal or plant resources. However, production of plant proteins can be challenging in regions with adverse geographical and climate conditions. Sheep production is an effective and sustainable mean to produce high-quality proteins with minimal detrimental impact on the environment when properly stocked and managed [4]. However, similarly to other livestock species, sheep are susceptible to endoparasite infections [5 - 7] and their presence is directly linked to reduction in livestock productivity [8] with parasite-infected animals exhibiting reduced efficiency on food intake and utilization [9, 10]. The effectiveness of commercial anthelmintics is declining due to the emergence of resistance, rendering the most common control measure for endoparasites increasingly ineffective [11]. This growing global anthelmintic resistance poses a threat to the sustainable production of animal protein for human consumption and, consequently, vaccination emerges as a potentially effective method to supplement anthelmintic control of gastrointestinal nematode (GIN) parasites. Moreover, consumers are increasingly concerned about meat production systems, demanding traceability and the reduction of chemicals in animal feeds. Although the technical benefits of chemical use in animal production systems are well-documented, the preference for chemical-free meat is growing globally due to concerns about chemical resistance and associated risks. To meet these demands there is a need for alternative and more effective measures to manage endoparasites.

Across breeds and even within a breed, sheep exhibit different levels of susceptibility or resistance to the GIN infections – which are modulated by their immune responses. Typically, resistant animals display earlier and more rapid immune responses, as well as higher counts of specific cells (eosinophils, mast cells, and globule leukocytes) compared to susceptible animals [12-15]. Modulation of the host's immune system stands as a long-term solution for eliminating endoparasites across the sheep industry. However, to develop an effective anti-parasite vaccine requires a comprehensive understanding of the immune responses established by the animals to expel the GIN. This review aims to discuss the characteristics of an effective immune response employed by ruminants to combat the GIN, with a particular emphasis on the roles of mast cells.

2. HOST RESPONSES TO PARASITISM AND THE ROLE OF MUCOSAL MAST CELLS IN IMMUNE RESPONSE TO PARASITISM

2.1. Host responses to parasitism

The immune responses used to protect the host from pathogens, such as parasites, can be innate or adaptive (Figure 1). The innate immune system protects an animal from parasitic infection in a fast, generic and non-specific way [6]; meanwhile, the adaptive system produces an antigen-specific response in order to eliminate a specific pathogen in a more effective way.

The innate immune cells include tuft, neutrophils, basophils, eosinophils, innate lymphoid cells, macrophages, and mast cells [16-20]. The innate immune system plays an important role in recognizing highly conserved pathogen associated molecular patterns through antigen presenting cells (APC) and is appropriately induced by pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns in order to initiate a protective adaptive immune response.

The immune system regulates host and parasites countermeasures against each other [21]. The colonization of gastrointestinal tissues by parasitic nematodes involves the damage and death of mucosal epithelial cells [22], resulting in signals from the damaged tissues, including the release of damage-associated molecular patterns (DAMPs)/alarmins [23]. Cells of the innate immune system at the site of parasite infection are activated by the DAMPs/alarmins in response to pathogen-induced damage and respond by initiating an inflammatory response as well as recruiting other immune cells to the infected sites through the secretion of cytokines (IL25, IL4) in the initiation of the very early inflammatory response [24] as well as other factors [25]. APCs such as macrophages, B cells and dendritic cells located at the site of infection, present antigens released from the parasite by the initial inflammatory response to T cells, thereby initiating the adaptive host response to parasitism. Parasite antigens must be released from the initial inflammatory response before phagocytosis by the APC, because the GIN are orders of magnitude larger than the APCs and therefore the pathogen cannot be phagocytosed (Figure 1).

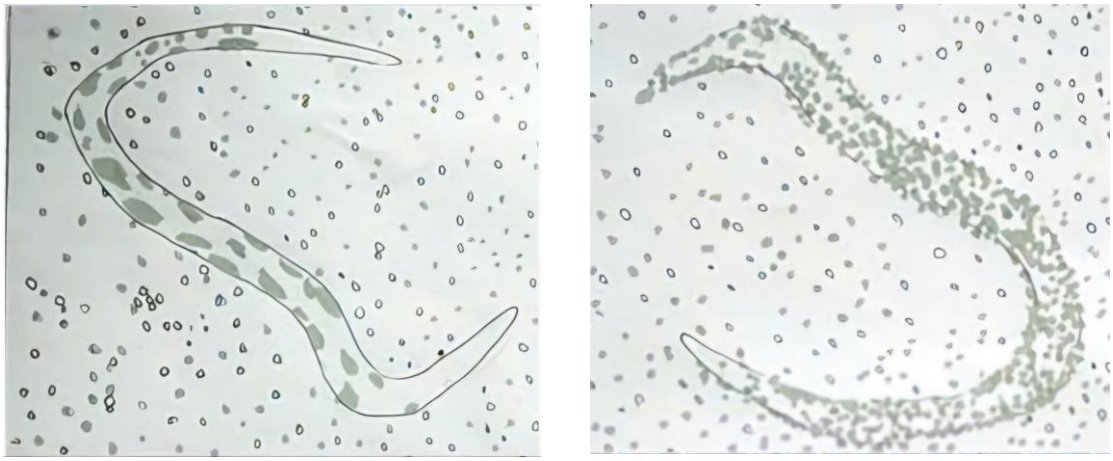

Figure 1. Engulfment of a nematode worm by immune system cells (predominantly eosinophils). The left figure illustrates the orders of magnitude differences in the size of host immune cells compared to the parasite. The right figure shows the immune cells coating the surface of the worm

The complement system that acts at the intersection of innate and adaptive immune responses in animal [26]. The activation of the complement system triggers a protease cascade that ends in opsonization and/or lysis of the pathogen [26]. Furthermore, the complement system are also involved in homeostatic processes such as removal of dying cells with exposed danger-associated molecular patterns that consequently generate a sterile inflammatory reaction [27]. The T cell mediated immune response type that is effective against the GIN is a T helper cell type 2 (Th2) response [12, 28]. The Th2 response along with B lymphocytes produces IgG, IgA and IgE antibodies. Parasites opsonisation by these parasite-specific antibodies facilitates antibody-dependent cell cytotoxicity (ADCC) type responses by effector cells which, upon activation, secrete cytotoxic agents such as leukotrienes, histamine and peroxides to paralyse the parasite.

On the other hand, parasites also have mechanisms to evade from host immune responses. For example, excretory/secretory (E/S) products (secretomes) released by the GIN *Haemonchus contortus* have a role in immune evasion; for example, examining excretory/secretory (E/S) microRNA (miRNA) and protein profiles from the mouse GIN parasite, showing that 73 proteins of nematode origin, and nematode protein secretomes revealed high conservation at the functional level [29], as reported for galectins affecting host peripheral blood mononuclear cell (PBMC) migration [19] and proteins such as Hcogalm/f [30], HcSTP-1 [31], miro-1 [32], and Hc-AK [32] inhibiting host T cells, contributing to the facilitation of immune evasion by suppressing the proliferation of host peripheral blood mononuclear cells (PBMCs) and the production of protective cytokines.

In sheep, several mechanisms influence the immune response against gastrointestinal GIN [33, 34]. The responses to nematodes also consist of inflammation and recruitment of mucosal mast cells and eosinophils [7], and both innate and acquired responses defend sheep from parasite invasion and maintain the immunologic homeostasis [35]. When the host is exposed to parasites, B cells are stimulated to increase and differentiate, generating copious amounts of antibodies. Meanwhile, memory B cells may be very important for vaccine mediated protection in parasitic diseases [36]. Effector memory T cells are found in peripheral tissues where they can respond immediately to pathogen-infected cell contact with effector activities [37].

Some experimental trials about the ability of sheep to eliminate the parasites such as Trichostrongylus colubriformis and Teladorsagia circumcincta showed that most of immune responses are Th2 responses [38]. Other assessments reported that immune responses to a variety of pathogen are mainly biased to the Th2-type [8]. The bias to Th2 is derived from the active enhancement of fetal Th2 responses to deviate maternal Th1 responses against the fetal allograft [38]. In response to GIN infection, mast cells also produce Th2 cytokines such as IL-13, IL-4 and IL-5 in addition to chemotactic factors which contribute to the recruitment of multiple inflammatory cells including eosinophils, natural killer cells and neutrophils [39]. In sheep, nematode-induced activation of mast cells has been associated with acquired immunity [40] and innate immunity [41]. Also, the GIN, which are multicellular parasites and complex pathogens, cannot be internalized by the phagocytic cells or the cytotoxic T cells of the immune system. Thus, the activation of various branches of the immune system, such as the T helper 2, is necessary [28, 42]. From that, the development of Th2 responses is strongly correlated to efficient immunity against the GIN in sheep, which is considered the main mechanism for parasite removal [43] and which can be fast acting or take several hours or days [44]. The efficiency of the GIN expulsion response depends on many different factors, such as mucosal mast cell and globule leucocytes, then mast cells, basophils, the T helper 2 and eosinophils are essential components in immune responses in order to kill parasites [45, 46]. Thus, the roles of eosinophils and mast cells in killing parasites need to be clearly understood to help the successful development of a future vaccine program to increase the production efficiency of livestock.

The eosinophils, basophils and neutrophils originate from blood and tissues [47, 48]. During normal cellular developmental processes in mice, mature cells are produced from bone marrow after 36-40 hours, but they are produced in about only 18 hours in animals infected with the GIN [49]. Some cytokines promote eosinopoiesis, with interleukin 3 and granulocyte macrophage inducing early precursor cell development, whereas T cells and mast cells produce IL5, which is a main cytokine for inducing increase and differentiation of eosinophil progenitors [50]. The proportion of peripheral blood eosinophil granulocyte leukocytes is 3-5% in the sheep [51, 52].

The major role of eosinophils in the immune system is against large pathogens which are unable to be phagocyted, such as the GIN [50]. Some substances such as immunomodulatory and pro-inflammatory mediators as well as cytokines are activated and secreted at the site of the GIN infection. These substances degranulate and release cytotoxic products. The eosinophils are involved in wound healing, tissue repair and antigen presentation [53, 54]. Histamine, collagenase, acid phosphatase and lysophospholipase are other enzymic components of eosinophils. The lysophospholipase role is not well understood but might be protective against toxicity of endogenous and parasitic lysophospholipids [50]. The cross-linking of surface receptors initiates this process after molecular binding of immunoglobulins and complement [55].

The Fc-receptors are regulated by gene expression, and they are present in the surface of different cell types such as eosinophils and antibodies, and the binding of antibodies to receptors is necessary to induce the degranulation process that kills the GIN [56-58]. Binding of the excretory component of the IgA induces powerful eosinophil degranulation [59, 60]. Several previous studies have reported the cytotoxicity potential of eosinophil granulocytes to the GIN [61]. Some parasites as schistosomula of S. mansoni [62], Fasciola hepatica cercaria [63] and Trichinella spiralis larvae [64] were morphologically damaged and killed by eosinophils in vitro. The granule residues, consisting of cytotoxic substances, promoted the morphological damage of the GIN's surface [65 - 67]. Eosinophils are important immune cells that have been implicated in resistance to the GIN infection in both naturally and experimentally infected sheep [68]. In addition, the sheep infected with the GIN show an increase in blood and tissue eosinophilia, implying that eosinophils may be and important mediator of host immune responses to the GIN [68]. Nevertheless, both phenotypic and bioinformatic evidence suggest that eosinophil activity against the GIN may vary among hosts [69]. Last but not least, stage-specific antibodies act in concert with effector cells, in particular globular leukocytes (intraepithelial mast cells) and eosinophils, appropriately activated/primed by type 2 (T2) cytokines, to initiate different mechanisms of GIN expulsion and killing [70]. In summary, eosinophils are important not only in protecting the host from the GIN infection but are also actively involved in eliminating and killing the GIN as well.

2.2. The characteristics and roles of mucosal mast cells in innate and adaptive immune responses to parasitism

Mast cells, which play a crucial role in the immune system to kill parasites, especially the IgE associated with the adaptive immune response, are originated from hematopoietic bone marrow. Mast cells along with eosinophilia are considered as a hallmark of parasitic infections [71], because mast cells can secrete different mediators such as histamine from their granules, as well as release of de novo synthesized lipid [72] and have active immune modulatory functions [73, 74]. Mast cells consist of many granules which are responsible for reactions involving in acute allergy such as vasodilation, increased permeability of vascular as well as contraction of smooth muscle and releasing toxicity to kill the GIN [75]. Therefore, they have important functions in the immune system and allergic responses as well as in response to certain types of parasitic infections. The contribution of these cells to the host's defense and immune regulation has wide application in the animal sector [37]. Animal models of parasitic infection have also illustrated that mast cells have crucial roles in host defense and survival of the host [76]. Therefore, the development of a mast cell line would be useful for effectively protecting the host against parasites, because the mast cells have some essential functions as follows: 1) capacity to rapidly and selectively generate suitable mediators to give out protective innate immune

responses and physiological responses, 2) ability to improve effector cell selection and 3) modifying responses to subsequent infection through antibody-relying activating and influences on adaptive immunity [37]. Scientific developments in recent years have allowed us to better understand the molecular mechanisms that underpin innate immunity that can contribute to the establishment of models of the mast cell response to parasites. Along with this understanding of the host's response, it is necessary to develop approaches for mast cells to respond to parasites to protect the host. Mast cells have a bean shaped nucleus and are large and round cells. Their cytoplasm consists of big granules with cellular staining [39, 45]. Mast cells come from hematopoietic bone marrow precursor cells [77]. Mast cell growth and differentiation depend on certain cytokines such as interleukin-3, interleukin-4, interleukin-9, and interleukin-10 [45, 75, 78]. The fibroblasts and bone marrow cells are sources of stem cell factor and some cytokines, such as interleukin 3, interleukin 4, interleukin 9, interleukin 10, induce growth of mast cells, whereas IFN-γ prevents proliferation of mast cells [79]. Furthermore, stem cell factor regulates migration of mast cells into tissues. Stem cell factor, also called kit ligand, controls apoptosis as well as mast cell mediator production and secretion [80].

Mast cells are considered crucial effector cells in responses associated with IgE of the adaptive immune system in allergic diseases such as asthma [81]. They are, along with gastrointestinal mastocytosis and eosinophils, considered parasitic helminth infection hallmarks [71]. Mast cells have the ability to release different mediators which are classified in three categories. While some mediators are preformed and remain stored in granules such as heparin, histamine, and enzymes mainly chymase and tryptase, others are de novo synthesized only after activation including lipid mediator leukotriene B4 (LTB4), leukotriene D4 (LTD4), prostaglandin D2 (PDG2), and platelet-activating factor (PAF), and the cytokines interleukin-10, interleukin-8, interleukin-5, interleukin-3, interleukin-1, GM-CSF, TGF-ß, VEGF, and TNF-α [82]. Therefore, these above cytokines/mediators are considered to have active immunomodulatory functions, for instance, inducing leukocyte migration and activation [83]. The activation is induced by crosslink between specific IgE binding with receptors that have high affinity on the surface of cell by antigens [39]. These activities result in releasing granules, synthesizing and secreting mediators of lipid as well as cytokines [84, 85].

The contents of the granules vary between species and different mast cell populations [39, 45]; however, in general they consist of heparin as well as sulphates of chondroitin that are considered as being substances that assist in binding and storing histamine and carboxypeptidases in the granules [80]. Histamine is responsible for reactions seen in acute allergy such as vasodilation, increases in vascular permeability, mucus secretion and smooth muscle contraction. Proteases can damage cells as well as promote complements such as the C3 and the C5 in order to produce anaphylatoxin of vasoactivity [39]. The C3 convertases cleave the C3 into the C3a, a chemoattractant molecule, and the C3b, which covalently binds to target surfaces and triggers phagocytosis. The C5 convertases cleaves the C5 into the C5a, a potent mediator of leukocyte recruitment and inflammation, and the C5b, the initiator of the membrane attack complex and cell lysis [86]. A variety of mediators with proinflammatory functions are synthesized by mast cells like some mediators of lipid originate from arachidonic acid and they are determined as a possible resource of other different cytokines as well as growth factors, for instance, interleukin 1 to 6, interleukin 8, interleukin 13, tumor necrosis factor α [80].

Parasitic infections often trigger not only strong innate and adaptive immunoglobulin responses but also in the abomasal mucosa responses, leading to the hypothesis that mast cells play a pivotal role in the host defense against parasites, such as intracellular protozoan and helminth parasites residing in the intestine, due to their activation through the high-affinity

receptor for the IgE [87, 88]. Research on mast cell deficiency in mice has indeed shown that mast cells can assist in the expulsion of the GIN [37]. Furthermore, mast cells have been found to provide protective effects against helminths in the intestine and various types of nematodes such as Nippostrongylus brasiliensis or Trichinella spiralis [89]. Recent studies have attempted to address this issue using various disease models. Murine nematode infection models have demonstrated an increase in the number of mast cells in the mucosa of the intestine during the GIN, and their activation is followed by the release of protease [89, 90]. Mast cell protease has been attributed to the expulsion of nematodes by disrupting the epithelial barrier through the degradation of the protein occluding tight junction [89, 90]. In addition, mast cells not only have a significant impact on the immune response of the host in protecting against bee venom but also play a more critical role in injured and infected sites [91]. Research has shown that mast cells in the skin control T cell responses in host defense against major Leishmania infections [92]. Furthermore, mast cells are crucial in controlling and enclosing parasitism, priming T cells at the sites of skin infections through the recruitment of dendritic and T cells and cytokine responses towards T helper 1. In fact, skin mast cells have been crucial for inducing the protection of the normal system, expressing resistance against parasitic infections [37, 80], as GIN can actively induce strong IgE responses. Recent studies have demonstrated that mast cells significantly contribute to defense in both IgE-mediated innate and adaptive immune responses against the GIN [93]. The mechanisms of mast cells are variable as they depend on the type and location of the GIN [91, 94]. An inflammatory response along with an increase in mast cell concentration has been considered a crucial factor in rejecting the GIN [46].

The gut is usually the first organ to come into contact with the GIN [95]. Studies have demonstrated that the number of mast cells in the intestinal mucosa increases after infection with Strongyloides venezuelensis or Trichinella spiralis due to the induction of cytokines [96-99]. Activated mast cells aid in expelling parasites, for example, through the creation of the chymase Mmcp-1 [100]. Additionally, mast cells can combat parasites residing outside of the gut. In the malaria disease model, mice injected with Plasmodium berghei-infected erythrocytes show mast cell control of infection through Tumor Necrosis Factor creation [101]. Mast cells also play a significant role in skin resistance against parasites like Haemaphysalis longicornis [102, 103]. Apart from their role in the innate immune response, mast cells also play a crucial role in the adaptive immune response. Mast cells exhibit crucial characteristics that contribute to the creation of an appropriate adaptive immune response at the infected site [104]. This not only aids in recovering from the initial infection but also enables a proper memory response if the same antigen is reintroduced to the host. Mast cells play an essential role in both immunoglobulin E (IgE) dependent and independent adaptive immune responses to the GIN [105 - 107]. They are also involved in the transition from innate to adaptive responses through interactions with dendritic, B, and T cells. Both mucosal and connective tissue mast cells play crucial roles in defense against intestinal parasitosis, as demonstrated in infections with Trichinella spiralis [108], Strongyloides ratti [109], Toxocara canis [110], and Heligmosomoides polygyrus [111]. The primary mast cell activation mechanisms in the immune response to parasites are mediated via Fcϵ RI and Fcγ receptors, as well as anti-parasite-specific IgE and IgG antibodies. This was demonstrated in H. polygyrus, Nippostrongylus brasiliensis, Strongyloides venezuelensis, and T. spiralis infections using IgE (-/-), IL-4 (-/-), or MC-deficient mice infected with the parasite in the presence or absence of parasite immune sera-derived IgE or IgG [112]. According to [113], the pattern of secreted mediators and changes in mast cell morphology indicate that the full signaling cascade of FcϵRI, characterized in response to allergens, is also activated by parasites (Figure 2).

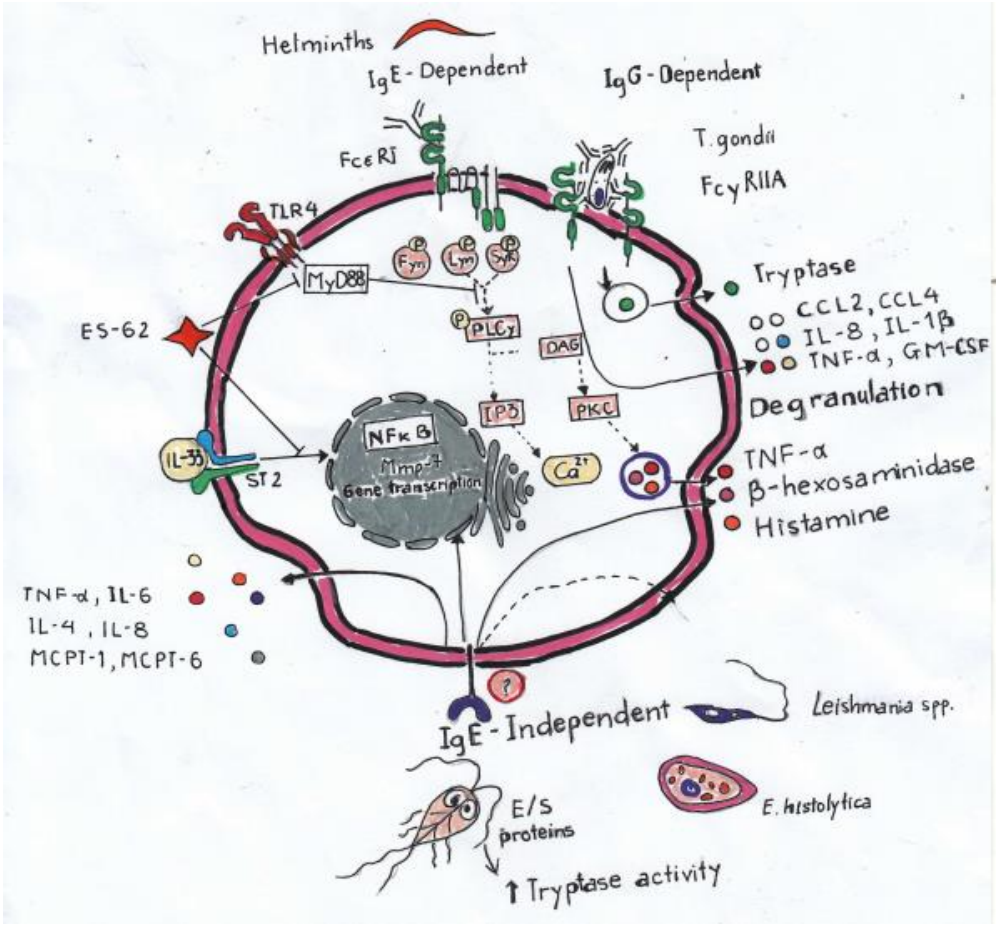

Figure 2. The pattern of secreted mediators and changes in MC morphology indicates that the full signaling cascade of FcεRI, which has been characterized in response to allergens, is activated by parasites

Vaccines against gastrointestinal nematodes of livestock have been extensively researched and developed by three international collaborations involving Australian research scientists. Using recombinant DNA technology, these collaborations have produced vaccines targeting Haemonchus, Trichostrongylus, and Ostertagia parasites. The identified protective antigens fall into two categories: 'conventional' antigens that stimulate naturally acquired immunity, and 'novel/covert/concealed' antigens that provide protection once immunity is induced through vaccination. To date, significant progress has been made, achieving 60 - 90 % protection against Haemonchus and other blood-sucking parasites using novel antigens. High titers of serum antibodies ingested by feeding worms lead to their demise. Ongoing research efforts are dedicated to unraveling the complexity of naturally acquired immunity, enabling the formulation and delivery of conventional antigens that can efficiently combat the GIN. Vaccines have successfully controlled infectious diseases, utilising the host's protective immune responsiveness to limit pathology and production loss. The recent success of BarbervaxTM, which achieves approximately 80 % protection against H. contortus through induction of high titres of antibody by repeated inocula of a native gut antigen preparation [114], raises the possibility for vaccination against other GINs. Therefore, vaccines effectively parallel the use of resistant animals/sheep, and reduce the frequency of drenching and pasture contamination [115]. This

research also suggests that to eliminate early stages of the GIN before they establish residence, the deliberate induction of hypersensitivity responses akin to asthma may be a desirable goal for vaccines. Remarkably, these two models share many common features [116]. In summary, mast cells play an indispensable role in immune responses to the GIN.

2.3. The role of Kit ligand and interleukin-3 in developing mast cell line in sheep

Cellular immortality occurs when cell-cycle checkpoint pathways (p53/p16/pRb) are impaired, telomerase enzyme is reactivated or upregulated, or certain oncogenes or oncoproteins are upregulated, leading to a higher rate of cell division [117]. Immortalization of cells from different sources and the establishment of immortal cell lines have proven valuable to understand the molecular pathways governing cell developmental cascades in eukaryotic cells, especially human cells. The breakthrough achievement of immortal cells and their critical importance in molecular biology has spurred intense efforts to establish cell lines that can elucidate the functions of telomerase, developmental lineage of progenitors, self-renewal potency, cellular transformation, differentiation patterns, and various bioprocesses [113]. Infinite cell lines have become one of the most favored experimental tools and play an irreplaceable role in cell-based biological research. Cell immortalization methods were reviewed by [118] along with a discussion on current progress in establishing immortalized cell lines in livestock and poultry and a comparison of the characteristics of several methods, with the aim of providing ideas to generate new immortalized cell lines. The development of mast cell populations in tissues is controlled by the combination of recruiting committed precursors, maturation of resident precursors, and local proliferation. Two growth factors, interleukin-3 and stem cell factor (KIT ligand), play important roles in developing mast cell populations [119]. For instance, a shortage of interleukin-3 limits the increase of mast cell populations during helminth infection [93], while the presence of Kit ligand helps increase the number of mast cells.

Therefore, in order to develop mast cell lines, it is essential to produce recombinant interleukin-3 and Kit Ligand proteins through a series of molecular biology tasks because mast cells require these proteins to grow in culture. Culturing a sheep mast cell line will enable researchers to understand the mechanistic role of mast cells in the innate and adaptive phases of the host's immune response to livestock parasites. This understanding can help with the development of vaccines that protect livestock from gastrointestinal parasites, thereby improving the economic viability of the sector. Interleukin-3 originates from T cells and other organs and plays a crucial role in linking the immune system with hematopoietic organs [120]. It is vital for the development, survival rate, and function of mast cell tissue [121], enhancing the host's immunological capacity against parasites. Studies on mice have shown that interleukin-3 can induce the development of immature mast cells in vitro [122]. Similarly, Kit Ligand can induce an increase in the number of mast cells and further differentiation of hematopoietic progenitor cells [123]. The interactions between interleukin-3 and Kit Ligand are especially important in enhancing the survival rate and maturation of mast cells [93, 124, 125] and may enhance the functions of certain effector mast cells [58]. Studies in mice have also illustrated that a reduction in the number of mast cells and the capacity for parasitic expulsion are strongly relevant to the deficiency of interleukin-3 and the Kit Ligand [113], indicating the essential role of interleukin-3 and the Kit Ligand in the host's immune response to the parasitic expulsive process. In sheep, interleukin-3 helps differentiate mast cells in the bone marrow [126]. In rodents, both interleukin-3 and the stem cell factor (Kit Ligand) play an important role in promoting the growth of mast cells in vitro [127]. The recombinant Kit Ligand can also induce the development of immature mast cell populations that rely on interleukin-3 in the in vitro

environment [128, 129]. Additionally, purified Kit Ligand from the supernatants of fibroblasts promotes the development of mast cells in mice, depending on interleukin-3 in the in vitro environment. Significant information about the factors affecting the development and maturation of mast cells has been achieved through culturing bone marrow-derived mast cells of mice in the *in vitro* environment with the presence of growth factors such as interleukin-3 and the Kit Ligand. The initial experiments evaluated the influence of growth factors on the growth and development of mast cells [130, 131], showing that the growth factors used in cultured media were responsible for the survival, maturation, and development of mast cells [78, 132]. Moreover, interleukin-3 also influences the phenotypic growth of mucosal mast cells in vitro [133]. The number of mast cells increased when cultured in a combination of interleukin-3 with bone marrow cells, and they exhibited transcripts for the subunit of FcƐ RI, which binds immunoglobulin E. The concentration of mast cells rose gradually, along with the FcƐ RI and transcription [134]. Therefore, interleukin-3 is essential for the development of mast cells from the progenitors of cord blood [135]. Meanwhile, the Kit Ligand also plays an important role in enhancing the survival rate and development of mast cells *in vitro* [125, 136]. In a study on primates, the Kit Ligand also induced the development of mast cells [137, 138]. Mutations in the functions of the Kit Ligand, which result in the activation of the Kit Ligand receptor, cause diseases such as mastocytosis and neoplastic disorders, leading to the expansion and accumulation of mast cells in humans [139]. It is evident that the development of mast cells strongly depends on the quantity and quality of growth factors such as the interleukin-3 and the Kit Ligand. Therefore, to keep sheep mast cells alive, it is necessary to produce a substantial amount of the Kit Ligand and the interleukin 3 in the culture.

3. CONCLUSION

In summary, mast cells play a crucial role in the immune system of sheep, encompassing both innate and adaptive immune responses. To develop a mast cell line, interleukin-3 and kit ligand are used to enable the perpetual growth of mast cells. Therefore, the successful cultivation of these cells holds great promise for the sheep industry, which has been significantly impacted by parasitic infections. This achievement could pave the way for protection sheep from gastrointestinal parasites, improving the economic viability of the sector, and contributing to the food security of communities that rely on sheep production to source protein.

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Declaration of competing interest. The authors declare that there is no conflict of interest in this paper.

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