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ROLE OF CYTOKINES AND CORRELATED CELLS IN HOST IMMUNITY AGAINST NEMATODE IN RUMINANTS

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Nematode contagion is a core impediment to the profitable dairy production for livestock farms. Gastrointestinal (GI) parasitism causes weight loss and low milk production, along with high mortality in sheep and goat. The current intensive anthelmintics therapies to control parasitic burden resulted in the appearance of drug resistant parasitic strains. Due to high demand of unadulterated animal products free from drugs motivated alternative strategies for improvement; including breeding plans for parasite control in ruminants. The increase of protective resistance to nematode infections, host genome show particular expression that is frequently confused by mechanisms concurrently essential to control multiple nematodes species as well as protozoan ecto-parasites, viral and microbial pathogens. The involved molecular mechanisms under these developments correspond to crucial steps toward improvement of efficient new parasite control strategies. Knowledge of various immunity methods of host and regulation of development of parasite, physiology, and virulence is able to identify the objective of parasite control. This review recapitulate current evolution and restrictions of optimistic regulatory biological pathways and genetic networks that concern with susceptibility and host resistance to infection of GI nematode in ruminants.

Keywords: Immunity, Nematode, Ruminants and cytokines.

INTRODUCTION

Ruminants (sheep, goats, cattle and buffalo) production methods are extensively constrained by GI nematode parasites species Cooperia, Haemonchus, Nematodirus, Oesophagostomum, Ostertagia, Trichuris, and Trichostrongylus, by reducing milk and effecting iron and haematological profiles especially among buffaloes during lactation period (Shahzadi *et al.*, 2014),

Ruminants (sheep, goats, cattle and buffalo) production methods are extensively constrained by GI nematode parasites species Cooperia, Haemonchus, Nematodirus, Oesophagostomum, Ostertagia, Trichuris, and Trichostrongylus, by reducing milk, meat, and fiber production worldwide (Miller and Horohov, 2006, Piedrafita *et al.*, 2010). Anthelmintic therapy is the major cost expensive current control practice in several farm enterprises. Conversely, the capability of parasites to develop resistance rapidly to these anthelmintic compound, mostly if animals are treated under defensive and suppressive treatment system, suggests alternative and sustainable control plans need adoption (Waller *et al.*, 1995, Jackson *et al.*, 2009). Sustainable control plans and procedures have been initiated to ruminant producers to extend the efficacy of anthelmintics as reducing the production losses caused by GIN parasite infections (Gray, 1997; Desoky *et al.*, 2015;Terrill et al., 2012). These guidelines/programs involve a mixture of non-chemical and chemical approaches to control GIN parasites effectively; conversely, the success of these programs is dependent on an ability to identify the parasitic problems qualitatively and quantitatively to calculate the severity of infection and the probable cost of production traits (Colditz, 2008, Athanasiadou et al., 2008). Alternatives solutions to anthelmintic application are also under examination for genetic control of the host to infectivity already in commercial appliance

www.nsip.org;http://www.sheepgenetics.org.au/;http://www.signetbc.co.uk/). Investigative assays that consistently evaluate the level of genetic control are essential for such applications.

Appreciative molecular methods that contribute to immune suppression, pathology and defensive immunity and the host resistance will have a massive impact on different control measures. We discuss here in review the result of the latest appliance of genomic tools for accompanying the regulatory genetic association and genetic pathways that define host susceptibility and resistance to GI nematode infectivity in ruminants.

***Innate Immunity*:** The correlation of GI nematodes and innate immune responses was poorly studied, other than the mucus production is controlled by goblet cells, act as physical barrier (Miller et al., 1981). Latterly, in our consideration the innate immunity dramatically expanded against GI nematodes.

The current re-classification and explanation of many distinctive population of innate cell (Spits et al., 2013) were motivated by identifying new population of cells, the innate lymphoid cells (ILCs) that generate (IL-5, IL-9, and IL-13) type 2 cytokines and consequently called ILC2s (Neill *et al.*, 2010, Turner et al., 2013) subsequent infection of GI nematodes in mice. Although several studies had demonstrated that the assistance of different cell population about innate immunity such as γδ T cells (Inagaki-Ohara *et al*., 2011), natural killer cells (Hepworth and Grencis, 2009) ILC2s play a crucial role for the control of GI nematodes (Hwang and McKenzie, 2013, Saenz et al., 2010a).On the basis of each cell, they emerge to produce cytokines in excess than T+CD4 cells (Hwang and McKenzie, 2013, Price *et al.*, 2010, Neill and McKenzie, 2011) and major population of cells generate cytokines in GI parasite infection (Neill *et al.*, 2010). Furthermore, bone marrow is the source of ILC2s can enhance protection efficiently (Neill et al., 2010, Saenz *et al.*, 2010b). Intestine and lymphoid tissue shows high production of ILC2 upon nematodes infection has also been demonstrated [*T.muris, T. spi-ralis* and *H. polygyrus bakeri*] (Grencis *et al.*, 2014, Filbey et al., 2014, Zaiss *et al.*, 2013). These cells have a defensive role sustained by the studies *H. polygyrus bakeri*, which confirmed that IL-1β stimulated after the infection was capable to decrease the ILC2s production and was correlated with the decrease of defensive immunity.

As a result from following studies, involve factor in creation of ILC2s have acknowledged a grand attention. Recent views enhance the idea of bone marrow ensuing originator discriminate locally under the effect of factors i.e Il-33, Il-25 and (TSLP) thymic stromal lymphopoietin secreted predominately from epithelium of intestine (Spits et al., 2013, Kang et al., 2012,

Zaph *et al*., 2007). Different signals from lungs like trefoil factor 2 (Wills-Karp *et al.*, 2012) and epithelial actl (an NF-κB-activating protein) in gut (Kang et al., 2012) are concerned in ILC2 response initiation in infection of GI nematode. All the subsets of ILC distinguish under the control of IL-7 (Klose *et al.*, 2014, Yagi *et al*., 2014), and verify that ILC2 existence at the barrier surfaces (e.g., intestine and lung) is constrained by IL-9 (Turner et al., 2013), a role of cytokine in enhancing type 2 immunity is well known (Faulkner et al., 1998, Faulkner *et al.*, 1997). In vivo application of IL-33 is a effective source of type 2 responses of cytokine (Schmitz *et al*., 2005, Humphreys *et al*., 2008) and may increase the discharge of GI nematodes (Humphreys *et al.*, 2008, Haraldsen *et al.*, 2009), while universally it does not emerge true (Grencis *et al.*, 2014, Yasuda *et al.*, 2012). Furthermore, in different studies of GI nematode infection IL-33R is deficient in mice shows that IL-33 may not be useful to control by receptor of membrane put the effects. Besides, infection of GI nematode studies in mice which is deficient in IL-33R designate that there is no need of IL-33 to activate from membrane receptor for applying its effects, by keeping its capability to function from different routes e.g., like a direct factor of nuclear transcription (Haraldsen *et al.*, 2009).

The protective role of IL-33 in infection of N. brasiliensis, after multiple infections in mice deficient in IL-33 the defensive mechanism is poor (Hung *et al.*, 2013). In helminth infection the natural function of IL-33 is not fully defined yet. Immunity of host impairs in different systems of GI nematode due to lack of IL-25 (Price *et al.*, 2010), however the administration of IL-25 cannot enhance defensive response in animal which are deficient in immunity as SCID mice (Owyang *et al.*, 2006), signifying that mechanism of adaptive response possibly essential to produce effective protection. Similar explanation has also been completed for IL-33 (Humphreys *et al.*, 2008) and includes the emergent indication of functional interaction between adaptive and innate cells (Hepworth *et al.*, 2013). However, ILC2 response may be important in animals which are immune deficient and, indeed, those animals which are deficient in nutrition (Spencer *et al*., 2014). It is striking consideration from different studies that environment of gut may play a crucial role by changing the baseline of ILC, may be via micronutrient and micro-flora. ILC2s have currently been stripped to articulate MHC class II and may play as (APCs) antigen-presenting cells (Hepworth *et al.*, 2013). An interaction between ILC2s and adaptive CD4+ T cell may be inferred from different studies which are effectiveness for protection is compromised particularly in the absence of CD4+T cells (Neill *et al.*, 2010). Current work has shown a discussion along MHC class II and CD4+ T by ILC2 is a significant part of IL-13 dependent clearance of N. brasiliensis (Oliphant *et al*., 2014).

Epithelial cells also produced TSLP, as the deficiency of it and its receptor may decrease the immunity produced by cytokine type 2 (Ziegler and Artis, 2010), as well as the capability to push out different GI nematodes for example T. muris (Taylor *et al*., 2009). In fact, intrinsic IκB kinase (IKK)-NF-κ B-dependent intestinal epithelial cell expression of gene plays a significant role in NF-κB pathway in T. muris infection during TSLP accredited to (DCs) dendritic cells to stimulate Th2 responses (Zaph *et al.*, 2007). Although, for different system (H. polygyrus

bakeri, N. brasiliensis) requirement of TSLP is not necessary, and impaired immunity did not in mice which is deficient in TSLPR (Massacand *et al.,* 2009). Even infection with T. muris in deficient TSLPR mice, impaired resistance may be inverted but IFN-γ were also deactivated, representing that maybe TSLP effects activate ultimately during down regulating Th17 and/or Th1 responses (Taylor et al., 2009). Therefore, the accessible data recommend a general idea in situation of innate immune defense to GI nematodes and responses of type 2 cytokine, while this may be perspective and nematode species reliant. Such as, T. muris varies from other nematode described beyond that it needs the stimulation of IFN-γ production and Th1 response for progress of chronic infection (Klementowicz *et al.*, 2012). The stimulation is not necessary for process of chronic infection by N. brasiliensis and H. polygyrus bakeri is effectively studied in mice for acute infection. Accordingly, the controlling mechanisms of chronic infection remained unclear in these species.

INDUCTION OF ACQUIRED IMMUNITY

***The Dendritic Cell*:** Even though during the infection of GI nematode the cytokines production is enhanced by ILC2s, their contributions and major task as APCs activity to make fully defined. It is proved from previous studies that for the resistance of GI nematodes the DCs are very important part of APCs population. In intestine DCs subsets are complex and may differ with intestinal vicinity. The studies about small intestine of murine based on, CD103+CD11 and CD103+CD11b+ highly populated which is enhanced by precursor DC, and CD103−CD11b+ a minor population which source is unidentified (Bekiaris *et al.,* 2014). Infections of GI nematode did not broadly defined with these newly illustrated phenotypes, but the infection is changed by the population of DC which is known. N. brasiliensis infection in intestine, increase draining of DCs in mesenteric lymph node and decrease in the proportion of $CD8\alpha^{int}$ $CD86^{hi}$ DC subset, with a complementary reduction in expression of CD86, CD103 and CD40 by DCs (Balic *et al.,* 2009). Furthermore, IRF4 is transcription factor necessary in DCs in production of Th2 responses mutually in lymphoid tissue of gut and lung in N. brasiliensis infection (Gao *et al.*, 2013). H. polygyrus bakeri infection is chronic, CD8α+ DC decrease in number clearly and emerged as a potential alteration in production of cytokines (Balic *et al.*, 2009). Moreover, ex vivo studies recommend that DCs of infected mice with H. polygyrus bakeri were decreased the production of CD4+ Tcell propagation in vitro but may enhance FoxP3+ Tcells levels than uninfected animals DCs (Smith *et al.*, 2011). Various studies revealed that infection with T. muris, influenced the host immunity by the movement of CD103+ DCs through CCL5 along with CCL20 in the epithelium of large intestine, the quick movement endorsing resistance and decrease movement related with liability and development of chronic infection (Cruickshank *et al.,* 2009). The importance of DCs, influencing the phenotype response is underlined by applying on mice, DCs of mice cannot stimulate (TGF)-β transforming growth factor due to lack integrin αvβ8 expression (Worthington *et al.,* 2013). With the infection of T. muris mice increased the immune response of type2 immunity, push out the parasite quickly, which shows the crucial role of cells in resistance.

While DCs are the APC canonical, infection of GI nematode showing different cell population, mainly the basophil (Voehringer, 2011) and ILC (Oliphant *et al.,* 2014), may play a significant antigen role. Goblet cells in intestine showed that transfer of antigen from gut to APCs (McDole *et al.,* 2012), and goblet cells secretes the mucines enhanced by DCs mutually antigens present in mucus, influenced by successive immune response (Shan *et al.,* 2013). Populations of innate cell and type 2 correlated have dictatorial influences on GI nematodes responses, including eosinophils and mast cells (Hepworth *et al.,* 2012, Nussbaum *et al.,* 2013), however possibly may not exert probably act as APCs.

***Correlation of different cells and Cytokines in immune responses of Ruminants* :** Parasitism naturally approach is employed by all parasite to stay alive in the ruminants. Parasites are capable to alter the immune response of host and maintain the persistent infection for a long time by examining the immune system and also by adjusting defensive mechanisms of host. The nematode infection has been characterized as a stimulus of T-helper cell in young animals that increases a vigorous Th2 response illustrated by a particular channel and pathways, associated with cells and cytokines. In infection the cytokine responses may play a key role in the development of vaccines and also provide a successful adaptive immune response to host. Furthermore, the important role of Th2 cytokines in nematode parasite infection may increase the immunity through intervention of immune system. Nematodes parasite can also increase the concentration of a Th1 response which is an important for the control of microbes and protozones, but Th1responses are down regulated by the Th2 responses (Finkelman and Urban, 2001) Fig. 1.

It is revealed that in murine models the GI nematode parasites induces the responses of CD4+ T cell which leads to enhancement and development of Th2 cells. The Th2 cells generate IL-4, IL-5, IL-9, IL-13, IL-25, and IL-33, narrated with stem cell source and TFG-β1, causes maturation and differentiation of eosinophilia, goblet cell and intraepithelial mast cells development (Artis and Grencis, 2008). These proceedings activate the goblet cells, enhance the turnover of enterocyte and also alter the permeability of enterocyte. IL-13 stimulates the goblet cells to enhance the mucus secretion and also prevent the epithelial surface from the attachment of parasites. whereas, Relm-beta and Muc5A secreted from different goblet cell are concerned with the responses for parasitic control (Artis *et al.*, 2004, Hasnain *et al.*, 2011) and increase the inflammation of mucosa (Li *et al.*, 2007, Nair *et al.*, 2008). Furthermore, IL-4 and IL-13 together stimulate macrophages that capture and increase the metabolic stress on larval phase of nematodes inside the submucosa of

intestine (Anthony et al., 2006, Artis and Grencis, 2008). The functions of epithelial cells and contraction of smooth muscles of intestine was controlled by the activated macrophages examined in mouse model (Zhao *et al.*, 2008). Local cytokines regulate a mechanism in which expulsion of parasite occurs and also increased turnover of enterocytes was found at the infected site of nematode (Cliffe *et al.*, 2005, Zaiss *et al.*, 2006). The Th1 responses at the time of nematode infection might be helpful in parasite resistance in different mouse strains (Else *et al.*, 1992), and various nematode strains can stimulate various host cytokine patterns that present the level of parasite load (Johnston *et al.*, 2005).

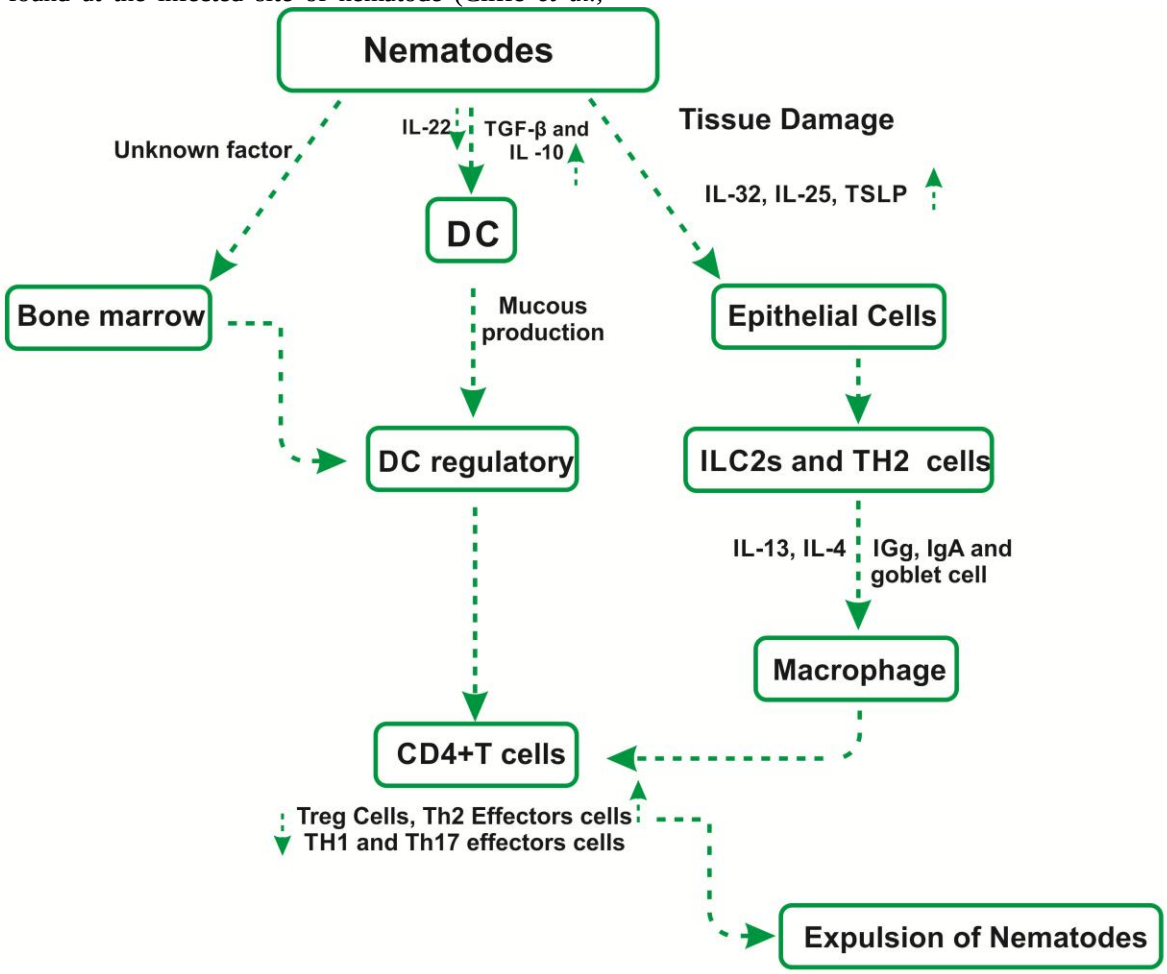

Figure 1: Mechanisms of effector CD4+ T cells and macrophages required for protective immunity to microbial pathogens. Specific stimuli characteristic of nematode invasion trigger different aspects of the overall type 2 immune response. (a) Induction of tissue injury by nematode induces the release of cytokine alarmins (IL-33, IL-25 and TSLP), which promote the production of TH2 cytokines by ILC2 cells and TH2 cells and also by eosinophils and basophils. Exposure of macrophages to IL-4 or IL-13 suppresses classical (M1) activation of macrophages and diverts their differentiation toward the M2 phenotype. (b) Excretory-secretory (ES) molecules produced and shed by worms can shut down DC synthesis of proinflammatory cytokines, chemokines and costimulatory molecules and also promote DC production of the immunoregulatory molecules IL-10 and TGF-β. (c) Nematode infection has also been shown to induce the in vivo differentiation of a CD103−CD11Clo population of regulatory DCs, which are inefficient in priming effector T cells and instead favor the generation of Treg cells. Together all these mechanisms act in synergy to produce a nematode modulated immunoregulatory environment that compromises TH1 and TH17 responses and favors Treg cell activities.

Th2-type in ruminants produces immune responses which stimulate the activation of mucosal mast cells and also act as a stimuli for the production of IgG and IgA, tissue eosinophilia, goblet cell hyperplasia, in response of GI nematode infection (Li and Gasbarre, 2009, Li *et al.*, 2010). Such as, eosinophils normally consist of <5% of whole leukocytes (Holtenius et al., 2004) but increase quickly at the place of infection as the infection start (Li and Gasbarre, 2009). Haemonchus placei (H. placei) obtain a typical distorted Th2-type resistant response in cattle. Expression of gene IL-13 and IL-4 in immune groups of Nellore cattle is robustly up-regulated then the susceptible groups (Zaros *et al.*, 2010). In a field study, naturally infected Nellore cattle with H. placei demonstrated that serum levels of IgE is found to be high (Bricarello *et al.*, 2007).

Furthermore, O. ostertagi infection in cattle shows an immune response with activation of both Th2 and Th1-type responses. Infections causes powerful secretions of IL-4 and IL-10 in abomasal lymph nodes (ABLN), the important site of antigen production, after eleven days

infection (dpi) adjacent to enhanced expression transcripts of IFN-γ, which were highly expressed ~25-fold over healthy cattle and remained hight through 28 dpi (Almeria et al., 1997, Canals *et al.,* 1997, Gasbarre *et al.*, 2001). ABLNs go through an extreme change in the group profiles of lymphocytes and a quick development of specific cell type following O. ostertagi infections. An enhanced in commonly TcR1+ cells and IgM+ (B cells), with the decline in proportion of T cells, was examined after infection. The enhancement in populations of B cell is reliable along strong antibody responses of serum and the production of IL-4 increased which is characterized by the infection of parasite (Canals *et al.*, 1997) and the enhancement population of TcR1+ cell may be constant for the observed highly expressed mRNA of IFN-γ. After many days of trickle infections with Ostertagia, the bull calves ABLNs showed characteristic of alteration from Th1 dominant response to a Th2 dominant response, illustrated by a decline in the expression of IFN-γ and IL-12, a strong enhancement in IL-4, IL-5, IL-10, and IL-13 (Claerebout *et al.,* 2005).The same response to trickle infection was examined in mice with a chronic infectivity with Heligmosomoides bakeri (Brailsford and Behnke, 1992). Though, the mucosa of abomasum of these infected cattle sustain characteristic of simultaneous responses of Th1 and Th2, distinguished by highly expression of IL-4, IFN-γ and IL-10. From these studies we conclude that features of a Th1 response are coordinated with the Th2 response during predictable infection.

Whereas, significant development in ruminant has been completed in accommodating cytokine responses during nematode infection, several questions remain unrequited. Cytokines innate immunity is contributory leads to enhance the defensive immunity and immune system of host remains satisfactory against infections. In ruminants, the efficiency of mucosal immunity is important for the control of nematodes infection. Certainly, immune sheep are highly capable in Th2 cytokines up-regulate than vulnerable sheep (Terefe *et al.*, 2007).

Moreover to cytokines, molecules emerge from cell adhesion may play a significant role in control of GI nematodes by increasing host immunity. Molecules of cell adhesion are necessary to interfere between cells and exchange of extracellular medium. The integrins, lectins, cadherins are molecules and proteins neural cell adhesions, are concerned with several biological differentiations, including cell production and progression, tissue framework and wound repair, pathogen identification and host protection (Li and Gasbarre, 2010). The inflammatory cells employment at the infection place is necessary for increasing a quick and efficient immune system, and may influence the expression intensity of Th1 to counter nematode infection (Bell and Else, 2008). The homing of mast cells to the mucosa of the small intestine is linked with Integrin-7. Integrins play a significant role in this procedure (Pennock and Grencis, 2006). For the stimulation of immune response lectins are important and related to inflammation (Lasky, 1991). C-type lectins, galectins and intelectins are distinguishing carbohydrates present on the surface of parasites. In innate immune responses the role of galectins have been recommended, together with helping as a pathogen receptors related to molecular patterns, contribute in cytotoxicity and stimulate several immune cells.

Additionally, it is reported that by the infection of nematode and protozoa generation of galectin-11 is occurred in the GI tract of cattle (Hoorens *et al.*, 2011). Moreover, by the infection of several parasites, such as Cooperia oncophora, O. ostertagia, and the protozoan parasite Giardia duodenalis, galectin-11 is highly stimulated in the gut of bovine (Hoorens *et al*., 2011), and Trichostrongylus vitrinus, *H. contortus* infections caused in sheep (Dunphy *et al.,* 2000). The expression of Intelectin 2 (ITLN2) is controlled by IL-4 (French *et al.*, 2007). Its prominent expression is examined in the sheep abomasum in effect of Dictyocaulus filaria natural infection, Teladorsagia circumcincta infection (French *et al.,* 2009), and *H. contortus* infection (Rowe *et al.*, 2009). This gene obviously erased in the genome of the vulnerable mouse strain, C57BL/10, however, present in the genome of mouse strain immune by nematode, BALB/c, signifying that ITLN2 may provide a defensive role in the innate immunity to parasite infection (French *et al.*, 2007). After the infection of ostertagia infection ITLN2 presence in abomasums is found to be significantly difference between resistant and susceptible heifers (Li *et al.*, 2011), and also found same pattern in abomasal mucosa between susceptible and resistant sheep after the infection of T. circumcincta (Athanasiadou *et al.*, 2008). Infected cattle with Cooperia demonstrate enhanced up-regulation of supplementary molecules of cell adhesion like collectin-43, cadherin 26, integrin, alpha 4, collectin-46 and lectin, galactoside binding inside small intestine (Li and Gasbarre, 2009). Furthermore, CDH26 is found to be highly expressed in correlation with FEC and eosinophils. Calcium dependent and intercommunication between the cells is important function of CDH26, it also belong cadherin family. Cattle have special collectins recommended for inflammatory reaction and also act as a first line of immune response for pathogens (Hansen *et al.,* 2002). After identification of collectins as PAMPs, causes neutralization, opsonization, phagocytosis and agglutination of pathogens (Gupta and Surolia, 2007). Simultaneously, confirmation suggested that the molecules of cell adhesion and cytokines are concerned in identification of carbohydrate present on cell surface of nematodes and remind an essential role of host immunity against nematode problems.

In latest study of cytokines IL2, IL4, IL13, and IFNG as a candidate gene were found be associated with FCE. The role of cytokine in immunity acts as small cell-signaling proteins, as well as participating as a medium of communication between cells. It is the pioneer study of candidate genes of the cytokine family (Bressani et al., 2014).

***Conclusion*:** In ruminants' nematode infection induce significant alterations in gene expression pattern at the place of infection and lymph nodes draining generally for the

control of molecules of cell adhesion and cytokines. Interaction between host and parasite has characteristic effects on mechanisms and associated expression of genes profiles. As well, the host demonstrated immune responses of various types that regulate temporally during infection, correlating with severe modification in parasite physiology, growth and virulence. Considerate the chronological effects immune responses of host through the period of nematodes parasitic infections will sustain the development of favorable approach in disease control. Furthermore, the enhancement of resistance and protective immunity to nematode infections depends on cytokines secretions. The control of parasites and increase mechanisms of host resistance, by breeding management to activates different pathways including cytokines.

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