

The Importance of Group 2 Innate Lymphoid Cells to Improve the Protective Immunity in Parasitic Helminth Infections

Méndez-Samperio Patricia 

Departamento de Inmunología, Escuela Nacional de Ciencias Biológicas, IPN. Prol. Carpio y Plan de Ayala. CD México 11340 México

ARTICLE INFO

Mini Review Article

VacRes, 2020

Vol. 7, No. 1, 50-53

Received: June 06, 2020

Accepted: September 06, 2020

Pasteur Institute of Iran

*Corresponding Author:

Prof. P Méndez-Samperio, MD, PhD
Departamento de Inmunología
Escuela Nacional de Ciencias
Biológicas, IPN. Prol. Carpio y Plan de
Ayala. CDMX 11340 México

Email: pmendezsamperio@gmail.com

Tel/Fax: (+55)5729600; ext 62499

KEYWORDS: Helminth infection,
Innate lymphoid cells, Th2 immune
responses

ABSTRACT

Helminthiasis is a neglected public health challenge worldwide. The relevance of the important role of group 2 innate lymphoid cells (ILC2s) in the protection induced by type 2 immune responses against helminth infections has recently regained attention. The parasitic helminth infections remain as a major public health concern worldwide, particularly in tropical countries in several areas of Africa, Asia, and South America. It has been demonstrated in the experimental mouse models that ILC2s induce significant secretion of type 2 cytokines and develop protective immunity against parasitic helminth infections. However, the effects of helminth-induced immunity mediated by ILC2s have not yet been clearly defined. This review discusses the current status of the researches related to the evidence of ILC2s to improve the protective immunity in parasitic helminth infections and how these cells promote parasitic helminth expulsion.

Citation:

Méndez-Samperio P. The Importance of Group 2 Innate Lymphoid Cells to Improve the Protective Immunity in Parasitic Helminth Infections. *vacres*. 2020; 7 (1) :50-53. DOI: 10.29252/vacres.7.1.50

INTRODUCTION

Parasitic helminths cause chronic infections that are a global public health problem with the outcome of important economic consequences [1, 2]. Numerous chronic parasitic infections are associated with the direct tissue damage [3, 4]. The helminths typically induce a type 2 immune response which is potentially protective [5-7]. During this immune response, stimulated epithelial cells exposed to the helminth antigens induce secretion of alarmins and cytokines including interleukins (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP). In the experimental mouse models, these molecules promote innate immune cell activation and induce the polarization of type 2 T helper (TH2) cells [8]. The immunity against chronic helminth infection produces a wide range of immune responses mainly characterized by the production of a type-2 immune response that involves the induction of TH2 cells [9-11]. This TH2 immunity has evolved as a major protective immune mechanism in parasitic helminth infection [12]. Interestingly, a potential communication between group 2 innate lymphoid cells (ILC2s) and different subsets of TH cells has been demonstrated to change towards a significant TH2 activation. The ILC2s are a family of innate effector cells including NK cells, and lymphoid tissue inducer cells, that secrete several cytokines such as IFN- γ , IL-5/IL-13, and IL-17/IL-22 which might promote the first-line defense against

helminth infection [13]. In 2010, the ILC2s were discovered through experimental mouse models in different helminthic infections [14, 15], while human ILC2s were initially described in 2011 [16]. These ILC2s induce classical TH2 cytokines in response to IL-25 and IL-33. A recent report showed that ILC2s induce a significant immunity against parasitic helminth infection [17]. It showed that ILC2s secrete IL-4, IL-5, IL-9, IL-10, and IL-13 cytokines during parasitic helminth infections. A more recent report demonstrated that ILC2s are involved in parasite expulsion in different helminthic infections as an important immunomodulatory pathway against several helminthic infections [18]. Currently, several studies have demonstrated the importance of ILC2s in promoting helminth-induced TH2 immune responses via release of the cytokines [19-22]. Alternatively, different subsets of TH2-associated dendritic cells are stimulated by the significant immunomodulatory pathways from ILC2s. It is important to consider that Tuft cells, ILC2s and epithelial progenitors induce a significant response circuit that mediates the epithelial remodelling associated with type 2 immunity. In this regard, after human helminth infection, tuft-cell-derived IL-25 further activates the ILC2s to secrete IL-13, which acts on epithelial cells to promote differentiation of the tuft cells. This immune response circuit is responsible for the initiation of the type 2

responses to helminths [23]. To date, the main regulatory mechanisms that mediate TH2 immunity against parasitic helminth infection are constantly enriched with new immunoregulatory molecules. This review will highlight emerging evidence indicating the current knowledge of the function and regulation of ILC2s to parasitic helminths and discuss how ILC2s enhance the control of innate and adaptive immune responses during TH2 immunity against helminths.

The Role of ILC2s in Enhancing Immunity Against Parasitic Helminth Infections

Group 2 innate lymphoid cells (ILC2s) are innate immune cells of the lymphoid lineage that are important mediators of type 2 inflammation during helminth infection. At present, innate lymphoid cells (ILCs) have been recognized as important mediators of the innate immunity to parasitic infections [19]. These cells are classified into ILC1s, ILC2s, and ILC3s according to their expression of transcription factors and cytokine production. To date, ILC2 progenitors have been recognized in different tissue samples such as the fetal liver [19]. The activation and proliferation of ILC2s after helminthic infections are controlled by several cytokines such as IL-25, IL-33, and TSLP, type 2 cytokines such as IL-4 and IL-9, or by inflammatory lipid mediators such as prostaglandin D2 [24-27]. In consequence, the activated ILC2s produce different cytokine molecules (IL-5, IL-9, and IL-13) which induce significant anti-helminthic immune responses. In this regard, the main molecular mechanisms that enable ILC2s to induce efficient triggering TH2 immune responses against helminths include the production of type 2 cytokine molecules. The IL-5-producing ILC2s induce eosinophilia [28-30]. In addition, IL-4 triggers B cells inducing isotype switching to IgE. Furthermore, IL-4 and IL-13 can also induce significant activation of macrophages [31]. Tissue repair is a subset of a broad repertoire of IL-4- and IL-13-dependent host immune responses during human helminth infection. The helminths induce a significant Th2 immune response, resulting in fibrosis and granulomas containing lymphocytes, and macrophages. During the late phase of helminth infection, the macrophages play an important role to counteract the inflammation caused by the Th1/Th17 immune responses [32]. Further, IL-13 in conjunction with IL-9 can activate mucus secretion [33] and regulate dendritic cells migration [34]. Interestingly, IL-9 can also act in an autocrine manner to activate ILC2s [35]. Further, ILC2-derived IL-9 has been shown to increase the immune cytokine production and significant activation of ILC2s following *N. brasiliensis* infection to produce an efficient worm expulsion [36]. In addition to their innate immunoregulatory effector pathways, the ILC2s lead to the creation of a significant adaptive immunity to induce an efficient parasitic helminth expulsion. In this regard, it has been shown that ILC2s interact with TH2 cells, which induce TH2 immune response and the IL-2 secreted by T cells might further improve the ILC2 responses against parasitic helminths. In particular, ILC2s express co-stimulatory molecules to activate T lymphocytes [37-40]. In this regard, the expression of the co-stimulatory molecule OX40L on ILC2s could induce tissue-restricted T cell co-stimulation that is important for Th2 and regulatory T immune responses against human helminth infections [41]. In addition, ILC2s increase type 2 immune responses and contribute to the parasitic helminth expulsion in an MHC-II-dependent pathway when transferred into IL-13-deficient mice [17]. In support of this, it has been demonstrated that ILC2s manipulate different TH2 immune responses in helminth infections [42]. Finally, the

ILC2-derived IL-13 has been reported to increase memory TH2 cellular immune response [43]. The crucial significance of the ILC2s linking the innate and adaptive immune response has important contribution to some aspects of the anti-helminthic immunity. Altogether, these immune mechanisms appear to act independently and/or concurrently to promote TH2 polarization against helminth parasites.

Some of the cellular and molecular mechanisms discussed here indicate the current knowledge of researches related to the important role of the ILC2s in enhancing immunity following *N. brasiliensis* infection and how these cells promote worm expulsion. Similarly, other studies have highlighted the critical role that ILC2s play in regulating immunity against other helminth infections. Specifically, recent studies demonstrated that ILC2 populations contribute to some mechanisms of the anti-helminthic immune responses against infection with *T. spiralis*, *H. polygyrus*, *Schistosoma* species, and *S. venezuelensis* [44-47]. In addition, increased ILC2s level in the patients infected with filarial worms has been reported. Interestingly, it has been proved in an experimental mouse model that excretory-secretory antigens of *H. polygyrus* diminished the production of TH2 cytokines by ILC2s. More recently, in the studies of ILC2s in the natural human helminth infection, it has been demonstrated that ILC2 proportions reduced during *Schistosoma* infection [48], indirectly indicating that the ILC2 proportions have a powerful impact on immune responses for the parasite survival. It is important to note that the current research efforts in immune-enhancing approaches to improve vaccination efficacy, might have significant impact on the human helminth infections. Better delineation of TH2 immune responses against parasitic helminths and understanding the induction and maintenance of the ILC2s as an important source of TH2 immunity to enhance protective immune responses will result in new approaches to control helminth infections.

CONCLUSION

The ILC2s are innate immune cells that accumulate in the tissues during helminth infection. The exciting ongoing research contributes to reveal the new aspects of ILC2s functions during helminth-induced TH2 immune responses. However, much more work needs to be done on this topic. In this context, there are some gaps in our understanding of how ILC2s intersect with the other host and pathogen-derived molecules to control various parasitic helminth infections. In addition, some of the studies discussed here have been conducted in the experimental mouse models of helminth infections, and these findings need more focus to see how ILC2s responses are controlled in helminth infection in humans. Lastly, more studies are needed to dissect how ILC2s responses could improve TH2 immune responses and contribute to the protective immunity against helminth infections. The critical new strategies to treat or prevent the parasitic helminth infections in humans will be addressed in the future studies.

ACKNOWLEDGEMENT

The author is a researcher of COFAA, EDI, and SNI.

CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

REFERENCES

- World Health Organization. Soil-transmitted helminth infections. 2019 [cited 2019 Aug 19]. Available from: <https://www.who.int/news-room/fact-sheets/detail/soil-transmitted-helminth-infections> [Google Scholar]
- Jourdan PM, et al. Soil-transmitted helminth infections. *Lancet* Published online September 4, 2017. [http://dx.doi.org/10.1016/S0140-6736\(17\)31930-X](http://dx.doi.org/10.1016/S0140-6736(17)31930-X)
- Brooker S, Clements AC, Bundy DA. Global epidemiology, ecology and control of soil-transmitted helminth infections. *Adv Parasitol*. 2006. PMID: 16647972
- Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. *J Clin Invest*. 2008 ;118(4):1311-21. doi: 10.1172/JCI34261.
- Anthony RM, Rutitzky LI, Urban JF Jr, Stadecker MJ, Gause WC. Protective immune mechanisms in helminth infection. *Nat Rev Immunol*. 2007 ;7(12):975-87. doi: 10.1038/nri2199
- Allen JE, Maizels RM. Diversity and dialogue in immunity to helminths. *Nat Rev Immunol*. 2011 ;11(6):375-88. doi: 10.1038/nri2992.
- Gause WC, Wynn TA, Allen JE. Type 2 immunity and wound healing: evolutionary refinement of adaptive immunity by helminths. *Nat Rev Immunol*. 2013 ;13(8):607-14. doi: 10.1038/nri3476.
- Méndez-Samperio P. Molecular events by which dendritic cells promote Th2 immune protection in helminth infection. *Infect Dis (Lond)*. 2016 ;48(10):715-20. doi: 10.1080/23744235.2016.1194529.
- Reina OM, Schreiber F, Benitez S, et al. Effects of chronic ascariasis and trichuriasis on cytokine production and gene expression in human blood: a cross-sectional study. *PLoS Negl Trop Dis*. 2011 ;5(6):e1157. doi: 10.1371/journal.pntd.0001157.
- Méndez-Samperio P. Immunological mechanisms by which concomitant helminth infections predispose to the development of human tuberculosis. *Korean J Parasitol*. 2012 ;50(4):281-6. doi: 10.3347/kjp.2012.50.4.281.
- Babu S, Nutman TB. Immunology of lymphatic filariasis. *Parasite Immunol*. 2014 ;36(8):338-46. doi: 10.1111/pim.12081.
- Allen JE, Sutherland TE. Host protective roles of type 2 immunity: parasite killing and tissue repair, flip sides of the same coin. *Semin Immunol*. 2014 ;26(4):329-40. doi: 10.1016/j.smim.2014.06.003.
- Kabata H, Moro K, Koyasu S, Kabata H, et al. The group 2 innate lymphoid cell (ILC2) regulatory network and its underlying mechanisms. *Immunol Rev*. 2018;286(1):37-52. doi: 10.1111/imr.12706.
- Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature*. 2010 ;464(7293):1367-70. doi: 10.1038/nature08900.
- Price AE, Liang HE, Sullivan BM, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci U S A*. 2010 ;107(25):11489-94. doi: 10.1073/pnas.1003988107.
- Mjosberg JM, Trifari S, Crellin NK, et al. Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR2 and CD161. *Nat Immunol*. 2011 ;12(11):1055-62. doi: 10.1038/ni.2104.
- Oliphant CJ, Hwang YY, Walker JA, et al. MHCII-mediated dialog between group 2 innate lymphoid cells and CD4(+) T cells potentiates type 2 immunity and promotes parasitic helminth expulsion. *Immunity*. 2014;41(2):283-95. doi: 10.1016/j.immuni.2014.06.016.
- Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat Immunol*. 2016 ;17(7):765-74. doi: 10.1038/ni.3489.
- Maizels RM, Hewitson JP. Myeloid cell phenotypes in susceptibility and resistance to helminth parasite infections. *Microbiol Spectr*. 2016;4(6). doi: 10.1128/microbiolspec.MCHD-0043-2016.
- Harris NL, Loke P. Recent advances in type-2-cell-mediated immunity: Insights from helminth infection. *Immunity*. 2017 ;47(6):1024-1036. doi: 10.1016/j.immuni.2017.11.015.
- Webb LM, Tait Wojno ED. The role of rare innate immune cells in type 2 immune activation against parasitic helminths. *Parasitology*. 2017 ;144(10):1288-1301. doi: 10.1017/S0031182017000488.
- Sorobetea D, Svensson-Frej M, Grecis R. Immunity to gastrointestinal nematode infections. *Mucosal Immunol*. 2018 ;11(2):304-315. doi: 10.1038/mi.2017.113.
- Gronke K, Diefenbach A, Gronke K, et al. Tuft cell-derived IL-25 activates and maintains ILC2. *Immunol Cell Biol*. 2016;94(3):221-3. doi: 10.1038/icb.2016.10.
- Wojno ED, et al. The prostaglandin D(2) receptor CRTH2 regulates accumulation of group 2 innate lymphoid cells in the inflamed lung. *J Immunol*. 2020 ;204(4):1001-1011. doi: 10.4049/jimmunol.1900745
- Huang Y, et al. IL-25-responsive, lineage-negative KLRG1(hi) cells are multipotential 'inflammatory' type 2 innate lymphoid cells. *Nat Immunol*. 2015 ;16(2):161-9. doi: 10.1038/ni.3078.
- Guigas B, Molofsky AB. A worm of one's own: how helminths modulate host adipose tissue function and metabolism. *Trends Parasitol*. 2015 ;31(9):435-41. doi: 10.1016/j.pt.2015.04.008.
- Molofsky AB, Savage AK, Locksley RM. Interleukin-33 in tissue homeostasis, injury, and inflammation. *Immunity*. 2015 ;42(6):1005-19. doi: 10.1016/j.immuni.2015.06.006.
- Sakamoto Y, Hiromatsu K, Ishiwata K, Inagaki-Ohara K, Ikeda T, Nakamura-Uchiyama F, Nawa Y. Chronic intestinal nematode infection induces Stat6-independent interleukin-5 production and causes eosinophilic inflammatory responses in mice. *Immunology*. 2004 ;112(4):615-23. doi: 10.1046/j.1365-2567.2004.01909.x.
- Yasuda K, Muto T, Kawagoe T, et al. Contribution of IL-33-activated type II innate lymphoid cells to pulmonary eosinophilia in intestinal nematode-infected mice. *Proc Natl Acad Sci U S A*. 2012 ;109(9):3451-6. doi: 10.1073/pnas.1201042109.
- Van Gool F, Molofsky AB, Morar MM, et al. Interleukin-5-producing group 2 innate lymphoid cells control eosinophilia induced by interleukin-2 therapy. *Blood*. 2014 ;124(24):3572-6. doi: 10.1182/blood-2014-07-587493.
- Molofsky AB, Nussbaum JC, Liang HE, et al. Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med*. 2013 ;210(3):535-49. doi: 10.1084/jem.20121964.
- Gordon S, Martinez FO, Gordon S, et al. Alternative activation of macrophages: mechanism and functions. *Immunity*. 2010;32(5):593-604. doi: 10.1016/j.immuni.2010.05.007
- Townsend JM, Fallon GP, Matthews JD, Smith P, Jolin EH, McKenzie NA. IL-9-deficient mice establish fundamental roles for IL-9 in pulmonary mastocytosis and goblet cell hyperplasia but not T cell development. *Immunity*. 2000 ;13(4):573-83. doi: 10.1016/S1074-7613(00)00056-x.
- Halim TY, Steer CA, Matha L, et al. Group 2 innate lymphoid cells are critical for the initiation of adaptive T helper 2 cell-mediated allergic lung inflammation. *Immunity*. 2014 ;40(3):425-35. doi: 10.1016/j.immuni.2014.01.011.
- Turner JE, et al. IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med*. 2013 ;210(13):2951-65. doi: 10.1084/jem.20130071.
- Mohapatra A, et al. Group 2 innate lymphoid cells utilize the IRF4-IL-9 module to coordinate epithelial cell maintenance of lung homeostasis. *Mucosal Immunol*. 2016 ;9(1):275-86. doi: 10.1038/mi.2015.59.
- Maazi H, Patel N, Sankaranarayanan I, Suzuki Y, Rigas D, Soroosh P, Freeman GJ, Sharpe AH, Akbari O. ICOS:ICOS-ligand interaction is required for type 2 innate lymphoid cell function, homeostasis, and induction of airway hyperreactivity. *Immunity*. 2015 ;42(3):538-51. doi: 10.1016/j.immuni.2015.02.007.
- Pelly VS, et al. IL-4-producing ILC2s are required for the differentiation of TH2 cells following *Heligmosomoides polygyrus* infection. *Mucosal Immunol*. 2016 ;9(6):1407-1417. doi: 10.1038/mi.2016.4.
- Halim TYF, Rana BMJ, Walker JA, Kerscher B, Knolle MD, Jolin HE, Serrao EM, Haim-Vilmsky L, Teichmann SA, Rodewald HR, Botto M, Vyse TJ, Fallon PG, Li Z, Withers DR, McKenzie ANJ. Tissue-restricted adaptive type 2 immunity is orchestrated by expression of the costimulatory molecule OX40L on group 2 innate lymphoid cells. *Immunity*. 2018 ;48(6):1195-1207.e6. doi: 10.1016/j.immuni.2018.05.003.
- Schuijs MJ, Halim TYF. Group 2 innate lymphocytes at the interface between innate and adaptive immunity. *Ann N Y Acad Sci*. 2018 ;1417(1):87-103. doi: 10.1111/nyas.13604.
- Halim TYF, Rana BMJ, Walker JA, Kerscher B, Knolle MD, Jolin HE, Serrao EM, Haim-Vilmsky L, Teichmann SA, Rodewald HR, Botto M, Vyse TJ, Fallon PG, Li Z, Withers DR, McKenzie ANJ. Halim TYF, et al. Tissue-Restricted Adaptive Type 2 Immunity Is Orchestrated by Expression of the Costimulatory Molecule OX40L on Group 2 Innate Lymphoid Cells. *Immunity*. 2018;48(6):1195-1207.e6. doi: 10.1016/j.immuni.2018.05.003
- Mirchandani AS, Besnard AG, Yip E, Scott C, Bain CC, Cerovic V, Salmond RJ, Liew FY. Type 2 innate lymphoid cells drive CD4+ Th2 cell responses. *J Immunol*. 2014 ;192(5):2442-8. doi: 10.4049/jimmunol.1300974.

43. Halim T.Y. et al. Group 2 innate lymphoid cells license dendritic cells to potentiate memory TH2 cell responses. *Nat Immunol.* 2016 ;17(1):57-64. doi: 10.1038/ni.3294.
44. Angkasekwinai P, Srimanote P, Wang YH, Pootong A, Sakolvaree Y, Pattanapanyasat K, Chaicumpa W, Chaiyaroj S, Dong C. Interleukin-25 (IL-25) promotes efficient protective immunity against *Trichinella spiralis* infection by enhancing the antigen-specific IL-9 response. *Infect Immun.* 2013 ;81(10):3731-41. doi: 10.1128/IAI.00646-13.
45. Halim TY. Group 2 innate lymphoid cells in disease. *Int Immunol.* 2016 ;28(1):13-22. doi: 10.1093/intimm/dxv050.
46. Angkasekwinai P, Sodthawon W, Jeerawattanawart S, Hansakon A, Pattanapanyasat K, Wang YH. ILC2s activated by IL-25 promote antigen-specific Th2 and Th9 functions that contribute to the control of *Trichinella*

- spiralis* infection. *PLoS One.* 2017 ;12(9):e0184684. doi: 10.1371/journal.pone.0184684
47. Shimokawa C, Kanaya T, Hachisuka M, Ishiwata K, Hisaeda H, Kurashima Y, Kiyono H, Yoshimoto T, Kaisho T, Ohno H. Mast cells are crucial for induction of group 2 innate lymphoid cells and clearance of helminth infections. *Immunity.* 2017 ;46(5):863-874.e4. doi: 10.1016/j.immuni.2017.04.017.
48. Nausch N, Appleby LJ, Sparks AM, Midzi N, Mduluzi T, Mutapi F. Group 2 innate lymphoid cell proportions are diminished in young helminth infected children and restored by curative anti-helminthic treatment. *PLoS Negl Trop Dis.* 2015 ;9(3):e0003627. doi: 10.1371/journal.pntd.0003627.